

Feasibility of Hybrid Conformal technique in treatment of Carcinoma Esophagus

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Aim of the study:

To assess the feasibility of Hybrid conformal technique in treatment of Esophageal cancers thereby achieving a non inferior dose distribution, to reduce the volume of lung treated, and also to calculate the time taken for both.

Materials and Methods:

Twenty patients with carcinoma Esophagus were taken and their treatment plans were analyzed. All the patients underwent baseline pulmonary function tests, and compared with the same after treatment. The CTV,PTV, spinal cord, heart, and the lungs were contoured and planned. Patients were treated with hybrid technique that combines CT based 2-opposing AP/PA technique and conformal beams. They were compared with the all-IMRT plans. Dose volume histograms were calculated for the planning target volume, heart, and lungs. Lung volumes were drawn with volume of the lung receiving 30 Gy (V20) and the mean lung dose (MLD) were calculated. The time taken for the all-IMRT and Hybrid-conformal techniques were calculated.

Results:

Analyzation of both the techniques showed that, taking into account, the constraints for organs at risk, and given the full dose to the planning target volume, the dose distributions achieved was not inferior to that achieved in all IMRT plans. Dose volume histograms revealed that V20 and mean lung dose was lower in Hybrid conformal technique than all-IMRT plans, which was found to be statistically significant with a p-value of <0.05 . The study also achieved cord and heart doses, as like the control plan. The time taken for Hybrid conformal technique was atleast 50% less compared to IMRT.

Conclusion:

Hybrid conformal technique will be a good alternative with which dose distributions achieved was not inferior to IMRT, along with reduction of both V20 and mean lung dose. The time taken for completion of treatment was also less compared to all IMRT plans, thereby leading to reduced treatment time. Reduction of lung doses might help in avoiding postoperative pulmonary complications like radiation pneumonitis, thereby improving the quality of life.

Key Words:

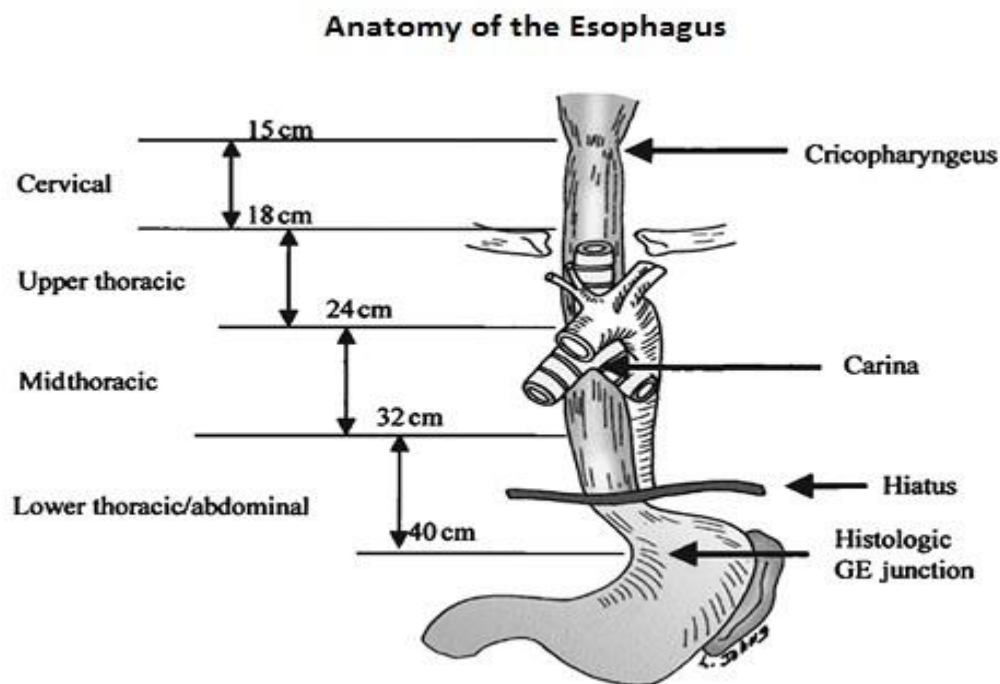
Esophageal cancer, Hybrid conformal technique, IMRT, Two opposing and conformal therapy, Radiation pneumonitis, Treatment related pneumonitis.

1.INTRODUCTION:

The esophagus is a hollow tubular structure, that bridges three compartments anatomically-neck, thorax and abdomen. It measures about approximately 25cm in length. It extends from the level of cricopharyngeus and extends upto gastro-esophageal junction. The esophagus is further divided into cervical and thoracic esophagus. The thoracic esophagus in turn, is divided into upper thoracic, middle thoracic and lower thoracic esophagus. The cervical esophagus extends from cricopharyngeus muscle upto the level of thoracic inlet, approximately 18 cm from the incisors. The upper thoracic esophagus, extends from thoracic inlet upto the bifurcation of trachea (carina), approximately 18-24cm in length from incisors. The middle thoracic esophagus, extends from carina, upto the level of inferior pulmonary veins, approximately 24-32cm in length from incisors. The lower thoracic esophagus, extends from inferior pulmonary veins, upto gastro-esophageal junction, approximately 32- 40 cm from incisors.

Spinal levels:

The spinal levels for the same classification is divided as , cervical esophagus from C7 to D3, upper thoracic esophagus, extending from D3-D5, middle thoracic esophagus from D5-D8, and lower thoracic from D9-D11 vertebrae.



Siewert et al Classification:

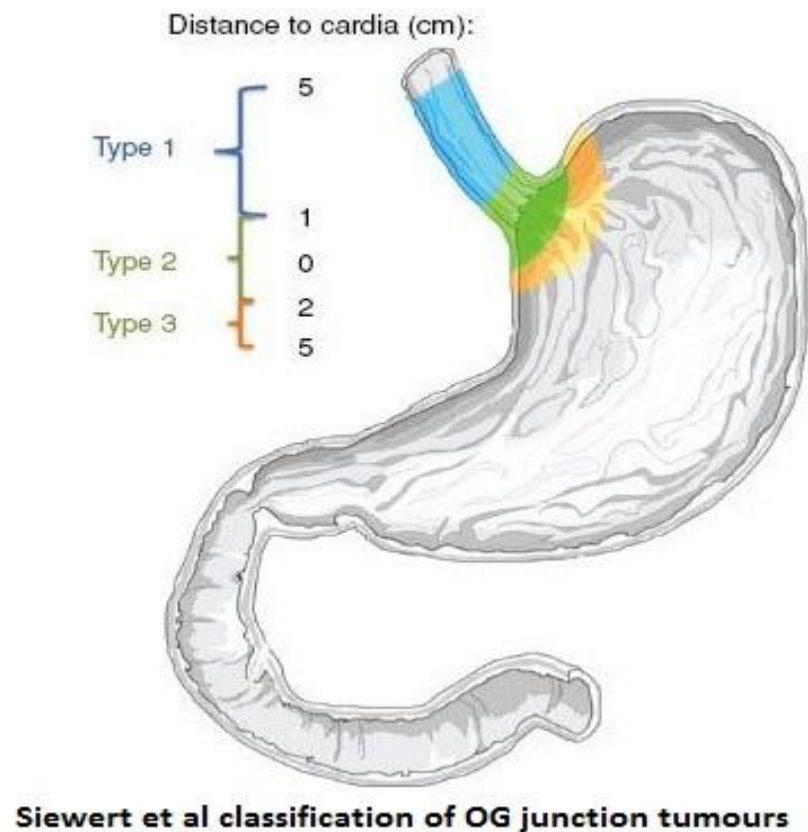
Siewert classified Adenocarcinoma of the gastro-esophageal junction, which often presents as a challenge for classification into esophageal or gastric cancers. The classification is based on demographics, histopathological variables, and also patterns of lymphatic spread. Based on these factors, Siewert et al classified OG junction tumours into three types: Type I tumours are those adenocarcinomas of the distal esophagus which often arises from an area which has intestinal metaplasia i.e. Barrett's esophagus, which may infiltrate the esophagogastric junction from above.

Type II tumours are those carcinomas that arise from the gastric cardiac epithelium or short segments with intestinal metaplasia at the esophagogastric junction. These tumours are also called as junctional carcinomas. Type III tumours are those that arise from subcardial gastric region which infiltrates gastroesophageal junction and distal esophagus from below. This was the original Siewert classification that was introduced in 1996. This classification was based on location of tumour and morphological characteristics.

International Gastric cancer association (IGCA) and the International society for Diseases of the Esophagus (ISDE) consensus conference that held in 1998, agreed that, the classification outlined above should form the basis for defining of disease, assessing the severity and reporting the results of treatment of adenocarcinoma that arises from the vicinity of gastroesophageal junction.

This classification was modified later by C.J.Shearer for classifying tumours conveniently. This was later known as Modified Siewert's classification that is being followed widely. This classification classifies tumours as Type I starting >1cm upto 5cm above the OG junction (Z line), and are known as Type I adenocarcinoma of the esophagus. Type II extends within 1cm from OG junction extends upto 2cm caudally. Type III tumours extends more than 2cm

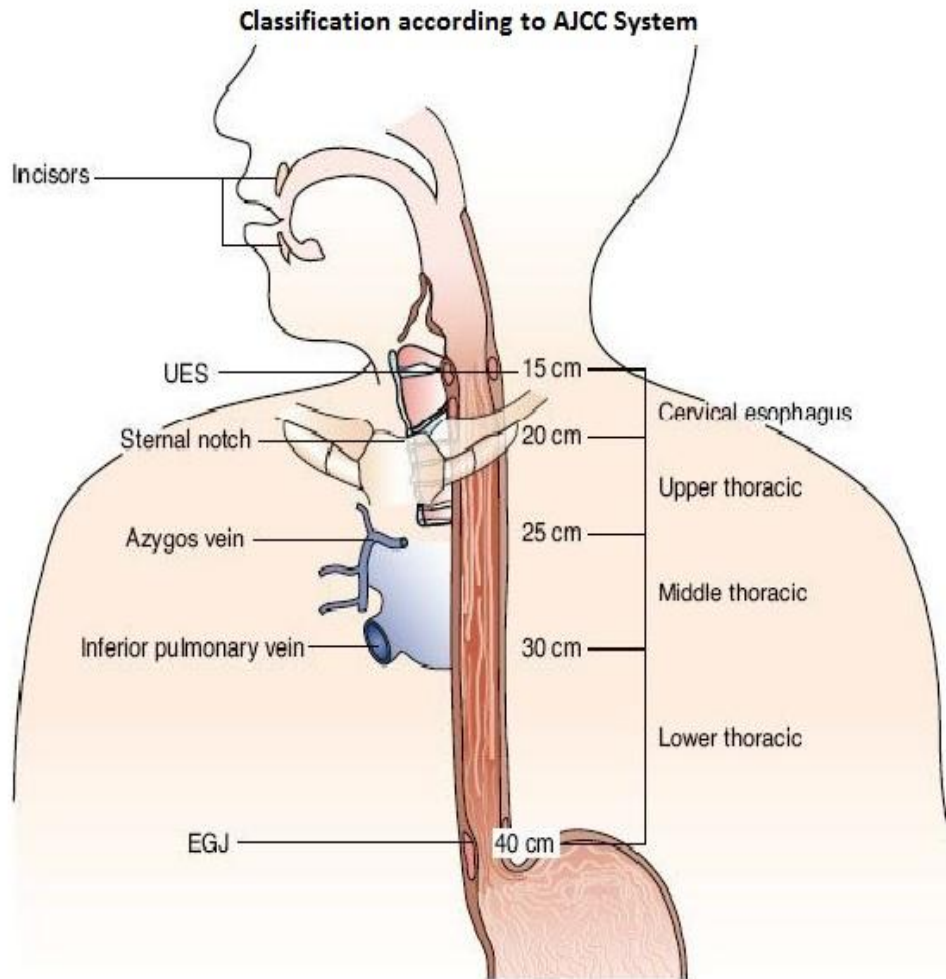
upto 5cm distally from OG junction. Type II and Type III are classified as gastric cancers.



AJCC classification:

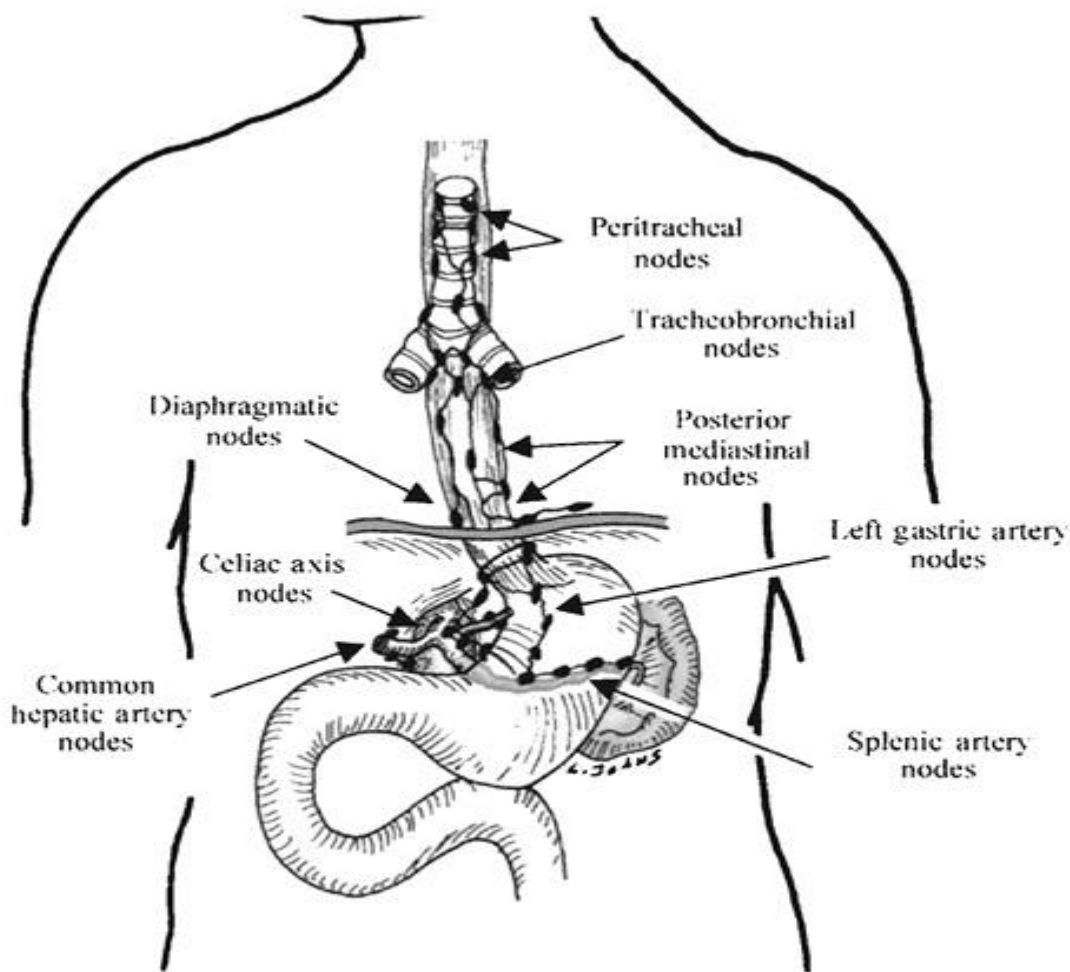
On the contrary, the recent classification given by American Joint committee on Cancer (AJCC), divides the esophagus as Cervical, which extends from the level of cricopharyngeus (C7 or 15cm from incisors), upto the level of thoracic inlet (approximately T3 or 20cm from incisors). The thoracic esophagus extends from T3 to T10 or T11. The upper thoracic esophagus

extends from thoracic inlet upto the level of lower border of azygous vein, extending approximately 20-25cm in length. The middle thoracic esophagus, extends from lower border of the azygous vein, upto the level of inferior pulmonary veins, extending 25-30cm from the level of incisors. The lower thoracic esophagus extends from the inferior pulmonary veins upto the level of stomach, inclusive of gastroesophageal junction. The Gastroesophageal junction can be accurately distinguished by means of squamo-columnar junction. The most recent classification also mentions that, if cancers having an epicentre, either in the lower thoracic esophagus, gastro-esophageal junction, or 5cm into the proximal stomach extending onto the gastro-esophageal junction or esophagus, are classified as Adenocarcinoma of the esophagus. If the epicentre is more than 5cm distal to the OG junction, or within 5 cm but not involving the OG junction, then they are classified as stomach cancers. Moreover, Siewert classification is disregarded in the latest AJCC classification. The AJCC classification is based on adjacent surgical landmarks.



Lymphatic Drainage:

The nodal system that drains the esophagus is essential in understanding the treatment approaches directed towards the various sublevels. Tumours of the cervical and upper thoracic esophagus, drains into cervical and superior mediastinal lymph nodes. Tumours of the middle third of esophagus drains both proximally and distally, and drains into paratracheal, hilar, subcarinal, periesophageal and pericardial nodes. Tumours present in the lower third of esophagus, drain mainly towards lower mediastinum and celiac nodal basins.



Lymphatic drainage of Esophagus

Due to the extensive lymphatic network, and because of the rich mucosal and submucosal drainage in the wall of esophagus, skip metastases are common. Tumours in the cervical and upper third can metastasize to celiac axis, and distal tumours can spread to cervical lymph nodes. In addition, around 71% of the frozen sections show negative margins, but show lymphatic micrometastases by immunohistochemistry . These nodal drainage usually drain following their arteries; viz inferior thyroid, esophageal, bronchial or the celiac axis.

Lymphnode involvement in percentage in various subsites:

Nodal drainage	Cervical (%)	Upper thoracic(%)	Mid thoracic(%)	Lower thoracic(%)
Cervical	14.2	8.0	6.2	5.2
Mediastinal	11.1	85.2	50.7	66.0
Abdominal	2.8	31.9	45.5	92.7

Radiotherapy:

The design and delivery of radiation therapy involves appropriate knowledge of the natural history of disease, anatomy, disease extent and nodal involvement, patterns of failure, and radiobiologic principles. Further, the use of proper equipment, implementation of methods to decrease treatment associated toxicity, proper coordination with the physicist and technological staff are essential.

General Techniques:

Depending on the primary tumour, there may be a number of sensitive organs that might come inside the radiation field. These include, which not only limited to , spinal cord, lungs, heart, intestine, stomach, kidney and liver. Hence, it is essential to reduce the dose to the normal structures to the utmost

minimum, without compromising the dose to the primary tumour and the loco-regional lymph nodes. These may be aided by means of simulation, CT planning and dose-volume histograms.

Conventional Therapy:

The target volume should include the primary tumour as defined by barium swallow and oesophagoscopy. It should include margins of about 5cm proximally and distally with the length not exceeding 18cm. The lateral margins should be enough to encompass the soft tissues surrounding the oesophageal wall (usually 6cm) or 8cm if adjacent nodes involved are to be included. In older patients, the superior and inferior margins can be reduced to limit the severity of acute radiation reaction.

Anatomical factors like spinal cord, lungs, heart, antero-posterior diameters constrain the delivery of homogenous dose distribution to the esophagus. The changing position of esophagus during its course, along with the variation of the contour of the body, often leads to the plane of treatment be inclined, rather than parallel to the couch. It should be borne in mind, that the created volume will be cylindrical in shape. The dose to the spinal cord and lungs should be reduced as much as possible.

The technique for the cervical and upper third of esophagus will include both the primary tumour and the supraclavicular lymph nodes. Various designs are possible and depends on the geometry of tumour and their relation to the spinal cord. The ideal design would be to design a three field technique that involves an anterior field and two posterior oblique fields. However, since the primary tumour is rarely midline, it is better to design with antero-posterior (AP) and postero-anterior fields (PA) to 39.6 and 41.4 Gy followed by right or left opposed oblique pair with photons to deliver upto 50.4Gy. Since this technique will exclude the supraclavicular fossa, a separate electron field is added to deliver at a depth of 2-3cm depending on the patient's anatomy, delivering thereby upto 50.4Gy. For middle and lower thoracic tumours, the same wedged single anterior and two posterior oblique fields are used.

Simulation:

The patient is placed supine with the hands resting above the head. Thin barium is used and the patient is advised to swallow the same. This helps in delineating the upper and lower borders of the field. Having defined the upper and lower limits of the field, and the width of volume, the patient is simulated from the side to define the depth in the anteroposterior plane. The field is inclined to exclude the spinal cord. It may not be possible always to exclude the spinal cord if the dose to the primary tumour should not be compromised.

During such cases, not more than 1cm of the cord should be included in the treatment volume. The posterior oblique fields are viewed to assess adequate coverage. Contours are taken through the top, middle and bottom of the volume. The positions of the spinal cord, heart, lungs and the tumour volume are measured. A correction should be done for the transmission of radiation through the lungs. (Usually, 3% per centimetre of lung traversed). The beam passing through the lung will give 30-40% higher dose to the oesophagus, than the same beam through the solid tissues. The dose to the spinal cord should not receive more than 40 Gy in 4 weeks.

Conformal therapy:

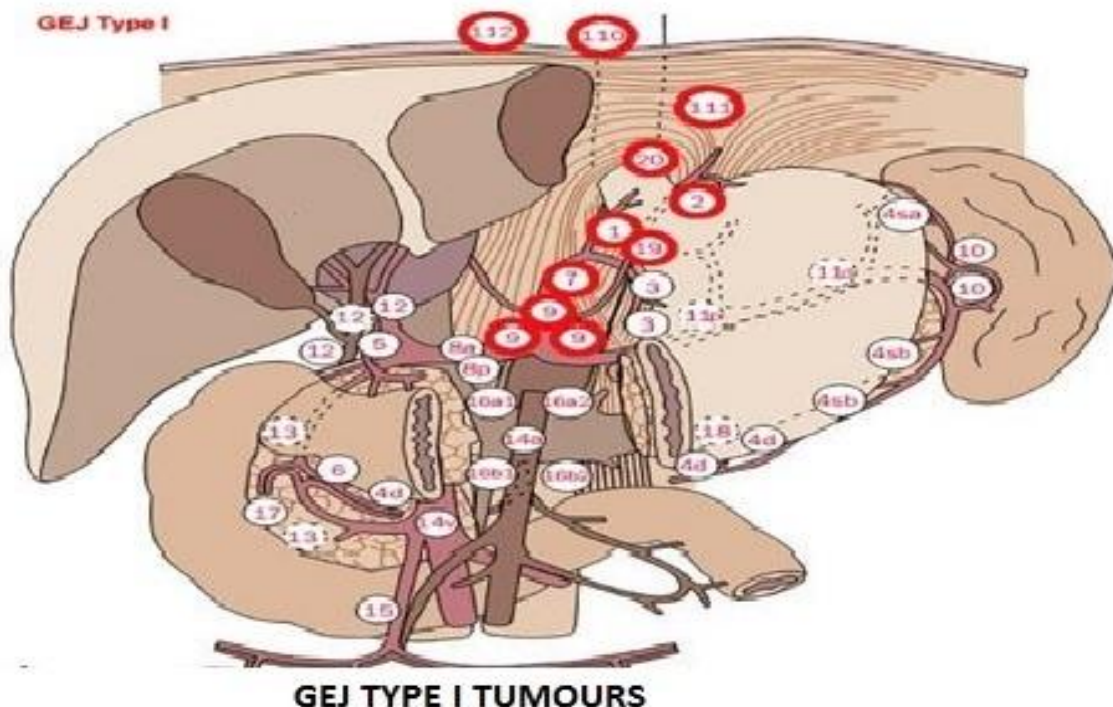
Three dimensional conformal therapy links 3D CT visualization of the tumour with the linear accelerator capable of shaping the beam both geometrically and by means of altering the fluence (Intensity modulated radiotherapy). 3D CRT encloses the target volume as close as possible and with minimizing the dose to the adjacent normal structures. The radiation oncologist as well as the physicist agree to the final planning target volume (PTV) which has been created by means of 3D growth algorithms, and protocols followed in the department, keeping in mind the organs at risk (OAR). This ensures understanding of the tumour cell density pattern within the PTV, homogeneity of dose distributions, dose constraints to adjacent OAR, avoidance of maximum

and minimum dose spots, and review of beam arrangements. Basic conformal radiotherapy consists of coplanar and static beams with the multileaf collimators (MLCs) or cerrobend blocks shaping the tumour volume. For coplanar non standard configuration of beams, Dose volume histograms (DVH) may aid in selecting the best plan; but it will not show whether the organ at question will receive a high or low dose. DVH of the CTV, PTV, PRV are all required to clinically correlate and arrive at the precise outcome. Selection of the final plan is made after scrutinizing the PTV and DVH. Good communication is important between radiation oncologist, physicists and the technical staff in ensuring no transfer or setup errors while delivering the treatment.

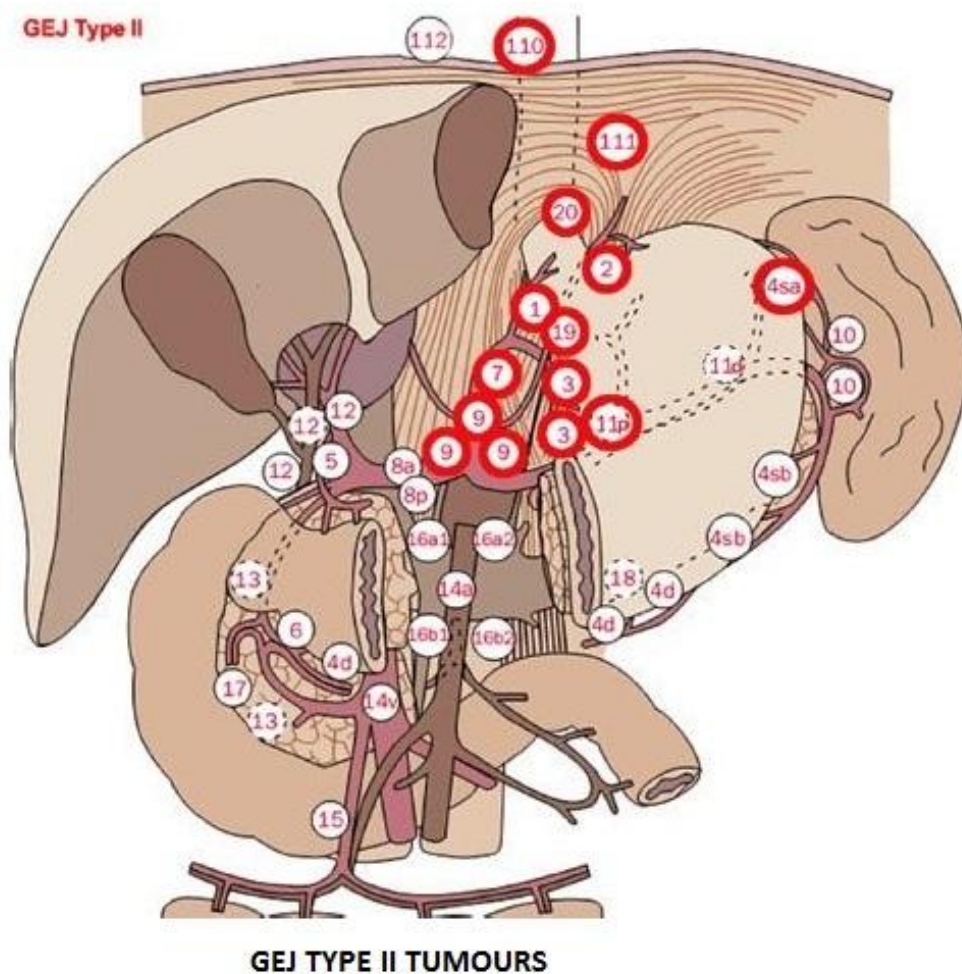
Conformal therapy involves the use of mixed beams like photons and electrons, and then the beams are modified using bolus, wedges, compensators, MLCs, shielding blocks. Optimization of skin dose is achieved by skin sparing using higher megavoltage energies, or by maximising skin dose with tissue equivalent material. Higher dose energy beams are used in treating pelvic patients, and lower dose is used for breast and head and neck treatments in adjusting skin dose to tumour dose as necessary.

Based on the tumour consensus and other patterns of spread data available for squamous cell carcinomas of esophagus, general guidelines for

field design can be as follows. For cervical and upper thoracic esophagus, the CTV encompasses nodal basins from the lower cervical region including the supraclavicular fossa superiorly upto subcarinal region inferiorly including the upper paraesophageal lymph nodes. For lower esophageal squamous cell carcinomas, lymph nodal basins from subcarinal region superiorly to the left gastric and common hepatic artery / celiac lymph nodal basins inferiorly. For middle esophageal tumours, field design should be individually tailored according to the tumour and complete coverage of paraesophageal nodal basins are necessary.



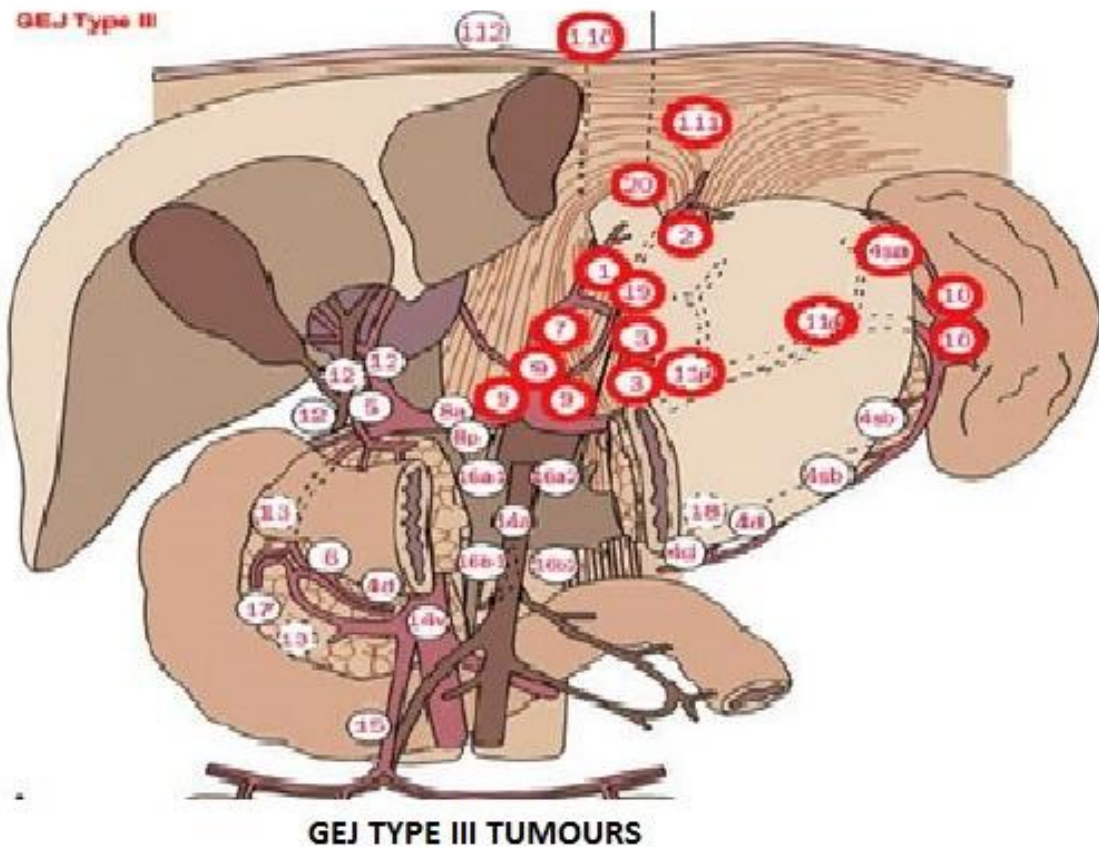
In the field design, potential nodal involvement and therefore, the target volumes may be problematic. Most reports state that more than 15% of metastatic nodes are 1cm away and that there is no obvious size difference between involved and uninvolved nodes. To add to this scenario, FDG-PET is only about 67% sensitive in detecting nodal metastases. Even, Endoscopic Ultrasound (EUS), which is considered as most sensitive in picking up lymphatic metastases, detects only about 75% of cases. Hence, these tests should not be relied upon exclusively for defining planning target volumes and understanding the nodal drainage is much important.



The field design for adenocarcinoma of esophagus, is similar to the lower thoracic squamous cell carcinoma, and deserves a special mention. Periesophageal lymph nodes are generally included for all patients. Because lymph nodal involvement is associated with more depth of penetration of tumour i.e T stage, and because gastroesophageal junction tumours are usually more advanced, inclusion of celiac lymph nodal basins for distal esophagus and OG junction tumours are usually indicated. Studies done by Erlangen et al shows some specific considerations. They are

- Lymphovascular invasion is predictive of nodal spread.
- Proximal extension of tumours beyond the Z line, and distal spread in type II and type III tumours predicts an increasing evidence of paraesophageal lymph nodal involvement.
- Estimated nodal incidence cut-off of 20% for inclusion has special considerations including:
 - The lower paraesophageal, paracardial, lesser curvature, left gastric artery nodes should be included in the CTV.
 - The presence of lymphovascular invasion predicts a nodal spread of more than 20% in left and right gastroepiploic, greater curvature, celiac trunk and splenic hilar regions.

- In T3/T4 disease, the gastroepiploic, greater curvature, celiac trunk, splenic hilar, splenic artery, common hepatic artery should be included.
- High grade tumours should include left gastroepiploic, greater curvature and celiac nodes should be included.
- Larger and deeply penetrating tumours should also encompass splenic hilar, splenic artery and also nodes along greater curvature.
- Tumour extending above diaphragm and those extending more than 1.5cm beyond the Z line should include midesophageal nodes upto carina. It should be borne in mind, that such extensive field will lead to potential side effects and hence the fields should be decided based on individual build and anatomy of the patient.



A margin of 5cm above and below the GTV with a 2.0-2.5cm radial margins are usually given to cover the submucosal and nodal disease. Because of the uncertainty of daily setup errors, and physiological organ motion (like peristalsis, respiration, cardiac motion), additional margin is given to the CTV, especially to the mobile distal esophagus. More recently, the Internal Target volume (ITV) is used to account for physiologic motion of the organs, which is usually encompassed in the PTV. Varying reports show that esophageal motion varies anteriorly and posteriorly from 0.1-4mm, lateral motion ranging from 0.3-4.2mm, and superior-inferior motion ranges from 3.7 to 10mm. An analysis evaluating interfractional right-left and anteroposterior movement shows that

left to right motion ranges from 1.8 to 5.1mm favouring leftward movement; and anteroposterior motion ranges from 0.6 to 4.8mm favouring posterior movement. It was concluded that 12mm left, 10mm posterior, and 9mm anterior margins are appropriate.

Intensity Modulated Radiotherapy:

IMRT is done using MLCs to define the beam intensity, independently at different regions of the incident beam, thereby producing the desired dose distribution uniformly, or deliberate non uniform dose distribution within the target volume. The position of the leaves can be modified in time with a fixed or a moving gantry. IMRT can be delivered by means of:

- Dose compensation
- Multiple static fields
- Step and Shoot technique
- Dynamic MLC
- Tomotherapy

In the Step and shoot technique, the sequence of static beams are used with the beam switched off between changes in position. In the dynamic MLC, there is automatic sequence of beam segments without stopping treatments. Other

methods like tomotherapy involves intensity modulated rotational delivery with the help of fan beams.

Forward planned or Segmental IMRT, involves simple tissue compensation with the beams eye view of PTV and the subsegments are shaped with different MLC to create a uniform dose distribution. Inverse planning requires dose to the PTV, CTV, OARs in terms of dose volume constraints, optimization of fluence, and 3D dose planning. Careful quality assurance is must in assuring the accuracy of the beam. Dose delivery is verified throughout the course of treatment by using radiographic films or EPIDs. Accurate patient positioning, target volume delineation, reduction of organ and patient movements especially respiration, validates the use of safe and precise IMRT dose delivery.

IMRT modulates the intensity of the beam and the geometric conformation, so that, it delivers complex dose distributions with the help of forward and inverse planning. Plans can be produced with concave shapes, and hence critical structures like spinal cord, etc can be spared better, thereby reducing the late toxicities of treatment. However, integral dose is higher, which is a drawback with IMRT, and hence increases the risk of development of second malignancies. IMRT with steep dose gradients, can lead to under dosage of tumour if margins are close and organ movements are present.

It is difficult to produce evidence of benefit for this new technology, until, wide randomized controlled trials are done to prove its superiority. Furthermore, the unwanted late effects of treatment cannot be predicted, and hence true efficacy of the treatment and to arrive at its therapeutic ratio, is delayed.

Organs at Risk (OAR):

The International Commission on Radiological Units (ICRU) defines OARs as those normal tissues, which lies adjacent to the tumour site, and may therefore be included in radiation fields, with a risk that radiation might lead to its impaired functioning. Hence, planning involves delineation of not only the tumour site, but also to avoid normal tissues.

There is a caveat that, increasing awareness of organ motion and treatment delivery errors might lead to larger PTVs which might overlap normal structures. In practice, the dose limits are usually applied to the organs at risk as defined on planning images. Among them, spinal cord serves as an exception, taking into account, the late effects of its toxicity, especially myelopathy and paralysis. The cord itself can be contoured, and a 3-5mm margins are added isotropically to create a PRV. Alternatively, the spinal canal can be contoured, which will automatically give a 0.3-0.5cm margin to the

OAR. Planning spinal canal is more advantageous, as it can compare the dose to that achieved in 2D planning, where spinal canal is always contoured.

In Cancers of the Oesophagus, the organs at risk, usually involves the spinal cord, lungs and heart. Hence, planning is done in such a way, that the cord dose is achieved, along with minimal doses to the lungs and heart. The cord dose is important compared to other structures, as the late effect that might occur with spinal cord is usually catastrophic, which will affect the quality of life. The other OARs are taken into consideration to avoid the dose as much as possible, which will reflect in reducing complications with multimodality treatment that is available at present.

Tolerance Doses:

To assess the acute and late morbidity of normal tissues, that might be affected by radiation., tolerance doses need to be set for each and every organ. Correlating the risk of side effects with 2D planning, the TD 5/5 was generated which is still in use. This gives an estimate of about 5% probability for a given side effect to appear after 5 years of treatment. Similarly, TD 50/5 assesses the 50% probability for a given effect to appear after 5 years of treatment. TD will usually assess the point dose, which are useful in organs like spinal cord. It may not be of much use, when the organs taken into consideration are made up of

parallel subunits, and hence, 3D volumes are drawn to assess the volume of tissue receiving radiation dose, which can be assessed by means of Dose volume histograms.

A dose-volume histogram plots radiation dose on the x-axis, and percent volume of structure of interest on the y-axis. The area under the curve and the shape of DVH is used to ensure homogenous dose is obtained for the target volume, with the dose received by the OARs is within acceptable limits. From this, the percentage of volume of dose received by the particular organ can be read as Vd.

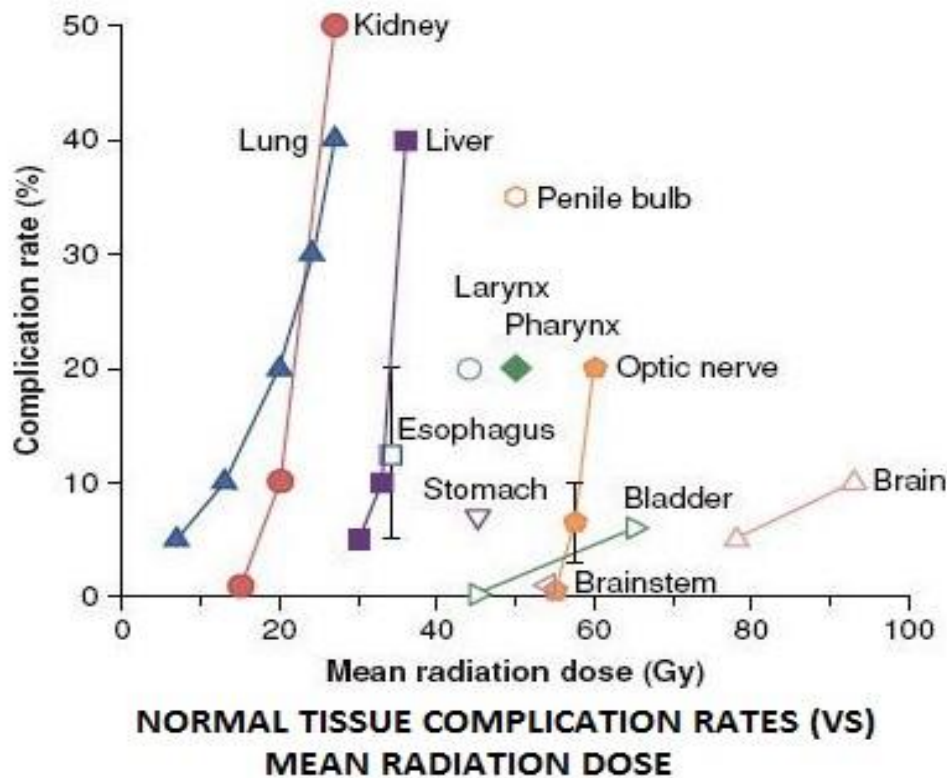
If DVH are obtained from series of patients in whom acute and late toxicities are recorded, then it may be useful to predict at what dose, these effects might occur. It must be borne in mind that these limits, essentially simplify the dose into a single value, and it must be correlated with doses from series of patients to arrive at a conclusion. Quantec data is used to arrive at the dose constraint in a better manner.

Clinical implications of QUANTEC AND EMAMI:

Two of the most commonly used systems for calculating dose volume limits are the QUANTEC and EMAMI; which has some of its own implications.

- ✓ Dose- response curves are different for different organs, indicating that there may be different mechanisms for radiation induced damage in different organs, and hence the endpoints will vary depending upon the mechanism.
- ✓ Some organs are considered to be in series; eg. spinal cord, small bowel and optic nerve, have a steep dose response curve beyond a critical dose threshold; and hence damage to a single functional sub unit can lead to dysfunction of entire organ. This is expected because of the anatomy and function of these organs.
- ✓ Moreover, some of the neural structures like brain, brainstem, optic nerve, spinal cord have similar kind of mechanism, with a TD of 55-60Gy, which corresponds to a Biologically equivalent dose of 100 Gy. In other words, it corresponds to an alpha/beta ratio of 3 Gy. As these structures are depending upon the vascular supply for each organ, it clearly implies that, vascular injury will be one of the most possible mechanisms for the above mentioned type of injury.
- ✓ Some organs are considered to be in parallel, for eg. lung, liver, kidneys, parotid; experience radiation induced damage at lower doses, and have a gradual dose response curves in contrast to serial organs. This suggest that, the mechanism of injury that occurs in these organs are different, and one possibility is that, each functional subunit inside the organ behaves differently compared to the structures inside the neuronal tissues.

Hence, to conclude, all such organs like the nephrons, hepatocytes can be radiosensitive.



- ✓ The concept of series and parallel is important, as the spinal cord has a serial component, and the lung has a parallel component. For example, in lung irradiation, doses to whole lung, if kept from 15 Gy to 23 Gy have a very low risk of developing symptomatic pneumonitis. On contrary, if it was heterogenous lung irradiation, then each lung behaves as a functional subunit, and hence, mean lung doses of 15 to 23 Gy to a single lung will have 10 % to 25 % chances of developing symptomatic pneumonitis. Hence, mean lung dose is just a tool to understand the percentage of lung receiving various doses of irradiation.

REPORTS	CONTRIBUTIONS	SHORTCOMINGS
Rubin et al, 1975	Introduced TD 5/5 and TD 50/5	Minimal dose volume data
Emami, 1991	Concise dose volume summary having most useful endpoints. Based on available clinical data and expert opinion.	Limited data available. More expert opinion.
QUANTEC, 2010	3D dose-volume/ outcome data. Systematic review addressing organ changes and confounding factors.	Not all organs have dose-volume data. Hence, cannot be used everytime.

Individual Organ tolerances:

Spinal cord:

As the effect of late radiation damage to the spinal cord is irreversible paralysis, treatment modalities that include spinal cord have always been cautious; and there is paucity of clinical data, to base on estimation of spinal cord tolerance. Therefore, estimates for the spinal cord have always been conservative.

The spinal cord should be either contoured as such, or given a 5mm margin to create the planning organ at risk volume (PRV). Dose to any part of the cord should be less than 46 Gy. If more than 15cm of the cord is treated, it should be less than 44 Gy. A small portion of the cord, may be 1cm can get a dose upto 50 Gy. In cases where hypofractionation are used, the dose to the cord should be lowered to reduce the toxicities. Other method is to calculate the point dose to the spinal cord, which should be less than 45 Gy.

Lungs:

Late fibrosis is best correlated with a V20 target value of less than 32% percent of the lung receiving less than 20 Gy. Mean lung doses are also used to calculate the constraints.

Risk of Second malignancies:

Any radiation dose that is been delivered, will theoretically increase the chance of second malignancy, and hence, safe dose limits to radiation cannot be prescribed. In practice, the irradiated volume should be kept as small as possible. This is better achieved with the help of newer techniques like the IMRT and VMAT. Even if techniques like IMRT, gives a better dose constraint to normal tissue, it delivers a higher integral dose, and hence, irradiates larger volume of normal tissue. This in turn, leads to increased risk of second malignancy. The long term data for IMRT is not available, and studies collaborate the risk only from biological modelling. The risk of second malignancies in Hodgkins lymphoma receiving mantle field radiotherapy, was estimated to be around 30% at the end of 30 years. Hence, long term follow up is necessary to conclude the best results of newer techniques.

Dose limits:

OARs:

- Spinal cord: Point dose of 45Gy
- Lung: V20 <30%

TD 5/5: 45 Gy (1/3), 30 Gy (2/3), 1750cGy (3/3)

TD 50/5: 65 Gy (1/3), 45Gy(2/3), 2450 cGy (3/3)

➤ Heart: V30 <46%

TD 5/5: 60Gy (1/3), 45 Gy(2/3), 40 Gy (3/3)

TD 50/5: 70Gy(1/3), 55 Gy(2/3), 50Gy (3/3)

Mean dose <26 to 30 Gy

2.REVIEW OF LITERATURE:

Radiation Therapy alone:

There are no studies comparing surgery vs radiotherapy as a sole modality of treatment. Radiation therapy alone is given in places where treatment is palliative and lesions are deemed inoperable because of the tumour extent and other contraindications. In general, those who receive radiation alone have a median survival of six to twelve months and a 5-year OS of <10%.

A meta-analysis of 49 series consisting of more than 8400 patients, treated with only radiotherapy, found overall survival at 1, 2 and 5 years to be 18%, 8% and 6% respectively. Hancock and Glatstein (7) reviewed around 9500 patients and found only 5.8% to survive at the end of 5 years. Another study by Okawa et al reported stagewise 5 year survival rate. For Stage I, 5 year OS was 20% , Stage II 10%, Stage III 3%, and Stage IV 0% with an overall survival rate at 5 years to be 9%. Lederman treated 263 patients with radiation therapy alone and reported 3-year and 5-year survival rates of 11% and 7% respectively.

Neoadjuvant Chemoradiation:

Preoperative radiotherapy to esophagus have some potential advantages:

- Increased resectability of tumours
- Increased radioresponsiveness secondary to increased tumour oxygenation
- Theoretical decrease in dissemination during surgery
- Avoidance of surgery in patients with rapidly progressive disease.

Walsh et al:

This study (8) compared the role of concurrent preoperative chemoradiation combined with surgery. A total of 110 patients of adenocarcinoma of esophagus were randomized to receive cisplatin, 5-FU, and concurrent radiation therapy followed by surgery vs surgery alone. Combined modality involved chemotherapy at weeks 1 and 6 followed by radiation therapy which included an anteroposterior and then changed to three field technique to a total dose of around 40 Gy in 15 fractions. Surgery was performed four to six weeks later. Median survival was 16% with preoperative chemoradiation therapy vs 11% with surgery alone. The 1, 2 and 3 year survival was 57%, 37% and 32% with multimodality therapy compared to 44%, 26% and 6% for surgery. Even though, the study concluded

neoadjuvant chemoradiation showed superior results, it was criticized for its poor surgery alone results, lack of follow-up and historical controls.

Urba et al:

This study (9) reported the results of 100 nonmetastatic esophageal cancer patients with squamous and adenocarcinoma histologies by comparing concurrent chemoradiation followed by surgery vs transhiatal esophagectomy alone. Chemotherapy regimen consisted of cisplatin, 5-FU, and vinblastine. Radiation included dose of 1.5Gy per fraction twice daily for three weeks to a total dose of 45 Gy followed by surgery on day 42. Tumours more than 5cm, Age more than 70 years, and squamous cell histology were associated with poor survival. There was no statistical difference at the end of 8 years, but the three year survival showed 30% vs 16% benefit respectively. There was reduced local recurrence with the results inclined towards concurrent chemoradiation followed by surgery (40% vs 16%), although the sample size was very small and hence could not be made as standard of care.

EORTC trial:

Bosset et al (10) randomized 282 patients with thoracic esophageal squamous cell carcinoma to either surgery or preoperative concurrent chemoradiation followed by surgery. Patients were treated with split course

radiotherapy, with a two weeks interval, giving 3.7 Gy to a total of 37 Gy. The study showed higher postoperative complications of about 12% compared to preoperative mortality of 4%. Also, there was disease free survival, negative margins, cancer related mortality and local control with neoadjuvant chemoradiation, but there was no overall survival. The study also concluded that higher dose per fractionation had a detrimental effect with wound morbidity.

CROSS trial:

One of the largest randomized controlled trials (11) that compared neoadjuvant chemoradiation followed by surgery versus surgery is the CROSS trial, or the Chemoradiotherapy for Oesophageal cancer followed by Surgery Study. This study included resectable tumours who received Chemotherapy with Paclitaxel 50 mg/m² weekly with Carboplatin (AUC-2), along with radiotherapy to a total dose of 41.4 Gy followed by surgery versus surgery alone. R0 resection was seen in 92% of patients in the chemoradiation arm versus 69% in surgery arm. Pathological complete response is seen in 29% of patients with chemoradiation. Median survival was 49 months in chemoradiation arm versus 24 months in surgery arm. The 3-year overall survival was 58% and 44% respectively. This study concluded that there is significant overall survival with preoperative chemoradiation, and the only

study to show the same, and hence can be considered as the treatment of choice for esophageal cancers.

Preoperative chemoradiation versus Preoperative chemotherapy:

German study group compared neoadjuvant chemoradiation with neoadjuvant chemotherapy by means of POET trial (Preoperative Chemotherapy or Chemoradiotherapy in Esophagogastric Adenocarcinoma). This study (12) randomized patients into two groups- first arm were randomized to receive cisplatin/ 5-FU based chemotherapy alone and second arm received similar induction chemotherapy followed by concurrent cisplatin/etoposide with 30Gy radiation therapy. This study was terminated earlier due to poor accrual. Even so, this study indicated that patients who were randomized to receive preoperative concurrent chemoradiation had:

- Higher N0 rates (64% vs 37%)
- Pathological complete response (16% vs 2%)
- Improved local control (76% vs 59%)
- 3-year overall survival (47% vs 28%)

Hence, the study concluded that preoperative chemoradiation had a better overall survival in locally advanced esophagogastric adenocarcinoma.

Chemoradiation vs Radiation:

RTOG 85-01:

This is one of the landmark trials that compared definitive chemoradiation against radiation therapy alone. Herskovic et al (13) randomized patients to receive radiation only to a total dose of 64Gy versus chemoradiation with a total dose of 50 Gy along with cisplatin and 5-Fluorouracil. Even though, chemoradiation arm received less dose of RT, there was significant advantage for the same, with a median survival of about 12.5 months for the chemoradiation arm vs 8.9 months, along with a 2-year survival rate of about 38% vs 10%. Local recurrence was decreased from 24 to 16 % and two year distant metastases was reduced from 26% to 12%. The study was stopped in between due to this high significant survival difference, and patients in radiation arm were transferred to chemoradiation arm. Updated results indicate 5-year overall survival rate of 26% vs 0%. Local recurrence was about 45% in chemoradiation arm vs 69% in radiation only arm; and distant metastases were 12% vs 40% respectively. Although there was statistical difference with chemoradiation, the rates of acute toxicity, including incidence of life threatening side effects of radiation like hematologic toxicity and fistula formation were more with concurrent chemoradiation versus radiation. Hence it was concluded that, local control, median and overall survival were better with

chemoradiation arm compared to radiation only arm, at the cost of increased side effects.

INT 0123 (RTOG 94-05):

This study randomized 236 cases of stages T1-4 N0-1M0 squamous or adenocarcinoma to either high dose radiation 64.8 Gy versus 50.4Gychemoradiation. Chemotherapy consisted of cisplatin and 5-Fluorouracil; Radiation field included superior and inferior margins of about 5cm above and below the tumour upto a TD of 50.4 Gy, followed by tumour boost to about 64.8 Gy with a 2cm margin above and below the tumour. No difference was found between high and low dose arms in median survival (13 vs 18 months), 2-year overall survival (31 % vs 40%) or local recurrence (56% vs 52%). It was noted that there was higher treatment related mortality with high dose radiation arm, but the same occurred before 50.4 Gy. Hence, the finding was found to be controversial.

Chemoradiation vs Chemoradiation followed by Surgery:

French study:

This study (14) randomized 445 patients, who were having clinically resectable tumours, involving both squamous and adenocarcinomas. All patients received cisplatin and 5-FU. Radiation were given as either 46 Gy over

4.5 weeks (continuous) or 30 Gy over two weeks with 15 Gy per week (split course). Among them, 259 patients who had partial response, were either randomized to surgery or additional chemoradiation with cisplatin and 5-FU. There was no significant difference between median survival (18 vs 19 months), 2 year survival (34% vs 40%) but the 2 year overall survival was better with surgery(67% vs 57%). The death rates were 9% with surgery arm and 1% with chemoradiation arm, along with a worse quality of life. The study concluded that, surgery in responding patients does not improve survival.

German study:

Another study (15) from Germany randomized 172 cases of potentially resectable squamous cell carcinoma of the esophagus with 5-FU,leucovorin,etoposide and cisplatin for three cycles followed by concurrent cisplatin and etoposide with 40Gy of External beam radiotherapy. The patients were further randomized to receive either surgery or additional chemoradiotherapy where the dose of radiation is increased to either 60 or 65 Gy, with or without brachytherapy. Although, there was increased local control in surgery arm, there was no overall survival between the two arms, and also, surgical arm was associated with severe postoperative complications (70%) and overall hospital morbidity rate of about 11%. It was found in regression analysis, that tumour response to induction chemotherapy was the only

prognostic factor. The only drawback of this trial was that around two-thirds of patients in surgery arm alone had surgery. The authors concluded that surgery only improves local control and not overall survival; and also, those patients who did not respond to induction chemotherapy might benefit from surgery, and hence apt tumour response should be noted and patients should be treated according to the same.

Adjuvant Chemoradiation:

North American Intergroup trial 0116:

This study was done to evaluate the efficacy of Postoperative adjuvant chemoradiation in locally advanced gastric and OG junction tumours. The study randomized 556 patients with the above mentioned malignancies to either surgery or surgery combined with postoperative chemoradiation. The multimodality treatment arm included 5-FU/ Leucovorin combined with radiotherapy to a total dose of 45 Gy followed by additional two cycles of 5-FU/ Leucovorin. Median overall survival was found to be 36 months vs 27 months favouring chemoradiation given after surgery. Also, the three year overall survival was 50 % in postoperative chemoradiation against 41% with surgery alone.

Brachytherapy:

Gaspar et al (16) examined and reported the results of intraluminal brachytherapy in patients with non-operable esophageal cancer in a randomized controlled prospective trial. Patients in this study, received 50 Gy of External beam radiotherapy followed by a two week break followed by brachytherapy. Patients then are randomized to either 15 Gy of High dose rate (HDR) brachytherapy in three fractions of 5 Gy each; or a single fraction of 20 Gy low dose rate (LDR) brachytherapy in a single fraction. The dose was then prescribed at 1cm from the source axis. Brachytherapy was accomplished by means of using 10- or 12-size French applicator, inserted through transnasally or transorally. The target length was defined by means of tumour length with a 1cm proximal and distal margin, which is measured by means of computed tomography, barium swallow, and endoscopy. Both external radiation and brachytherapy were given concurrently with 5-FU chemotherapy. The dose in HDR arm was reduced to 10 Gy in two fractions due to the development of fistulas in two patients. The LDR arm was closed because of poor accrual. There was a 11 month median survival in both arms. Local residual disease or recurrence was found in 63% of 49 patients treated, and six patients among them had developed esophageal fistulas. Among these six patients, three patients, had treatment related deaths. It was found that there was 18% chance of developing fistula at the end of one year. Other studies showed fistula

development rate of about 0-12%. It was concluded that, concurrent chemotherapy along with brachytherapy have increased morbidity, and should be approached with extreme caution depending on the patient.

Brachytherapy as a palliative modality:

Most of the advanced non-operable esophageal cancer patients, present with total dysphagia. To relieve the same, either a metallic expanding stent or brachytherapy is commonly used. Danish study compared the results of palliation for endoscopic stent placement versus single dose HDR brachytherapy. This study randomized 209 patients, and the exclusion criteria were as follows:

- Tumours more than 12 cm.
- Tumours within 3cm of upper esophageal sphincter
- Deeply ulcerated tumours
- Tracheo-esophageal fistula
- Tracheal involvement
- Patients with pacemakers
- Patients with stent placement
- Patients treated with radiation treatment

Brachytherapy was delivered by means of a 1-cm flexible applicator through which a single fraction dose of about 12 Gy is delivered, which is prescribed at a distance of 1cm from the source axis. This study showed that, patients who had stent insertion had an immediate relief for dysphagia, but on the long run, those patients who received brachytherapy, had a long term relief from dysphagia compared to endoscopic stent placement. Also, complication rates were higher, including bleeding from stent placement in stent arm vs brachytherapy arm (33% vs 24%).

Toxicities:

Postoperative complications:

- ❖ Pulmonary complications
- ❖ Cardiac morbidity
- ❖ Leak at anastomotic sites
- ❖ Recurrent laryngeal nerve paralysis
- ❖ Stricture formation (14-27%)

Radiation induced Toxicity:

Acute Toxicities:

- ❖ Esophagitis
- ❖ Dysphagia

- ❖ Neutropenia
- ❖ Thrombocytopenia
- ❖ Epidermiditis
- ❖ Fatigue
- ❖ Weight loss
- ❖ Nausea
- ❖ Vomiting

Some of the life threatening complications in addition to above are Perforations of esophagus, which presents with retrosternal pain, fever, thready pulse, shock, hemorrhage, etc. The addition of chemotherapy increases the risk of side effects mentioned above, atleast increasing in about 50-70% of patients. In fact, the risk of grade 3 toxicity increases to about 44% compared to 25% with radiation therapy alone. Grade 4 toxicity is shown to be 20% with concurrent chemoradiation in contrast to 3% with radiation therapy alone. The percentage is less, because the number of patients with such toxicities may not survive the same.

Late Toxicities:

The most common late effects associated with radiotherapy are stenosis and stricture formation. Dysphagia associated with stenosis and stricture occurs in about 10-15% of patient, and can be relieved by Savary-Gilliard dilatation,

as a temporary basis. Usually three to four dilatations will be required. RTOG trial showed that long term side effects especially Grade 3 toxicity are nearly equal with both concurrent chemoradiation and radiation therapy (29% vs 23%). However, Grade 4 toxicities are more with concurrent chemoradiation arm (20%) versus radiation arm (3%).

Radiation pneumonitis:

One of the most common under reported complications is Radiation pneumonitis. It can range from minimally symptomatic to fatal disease. The most common presenting features are non productive cough, dyspnea, respiratory distress, etc; which occurs mostly after two to six months of radiation therapy. Some of the most common predictive markers to assess lung toxicities are V20 > 30 percent, mean lung dose of more than 20 Gy, V5 of more than 42%, or an absolute V5 of more than 3000 sq.cm.

Grading:**Radiation Therapy Oncology Group Criteria (RTOG)(17):****Acute:**

Grade 0	No change
Grade 1	Mild symptoms like dry cough and dyspnea on exertion
Grade 2	Persistent cough requiring narcotics/antitussives; dyspnea with effort but not at rest.
Grade 3	Severe cough requiring antitussives, dyspnea at rest, Radiological changes of patchy pneumonitis, might require steroids or oxygen.
Grade 4	Severe respiratory compromise requiring assisted ventilation.

Late:

Grade 0	No change
Grade 1	Mild symptoms like dry cough with mild changes radiologically
Grade 2	Moderate symptoms like fibrosis and pneumonitis. Presents with severe cough, patchy radiological

	changes, fever
Grade 3	Severe fibrosis, Dense radiological changes
Grade 4	Severe respiratory insufficiency, continuous assisted ventilation with oxygen.
Grade 5	Death

Trials from Japan, showed that, in patients (18) treated with concurrent chemoradiation with cisplatin and 5-FU, reported an incidence rate of 27%. The study also concluded that risk of radiation pneumonitis can be judged when V20 was more than 30%. Similarly, in a study done by MD Anderson Cancer Center, 101 patients were studied which included both operative and nonoperative patients having distal esophageal/gastroesophageal junction tumours who underwent a combination of both 3D CRT and IMRT, reported a risk of 59% , 5% and 1% of grade 2, 3 and 5 radiation pneumonitis respectively. On similar aspects, another study from Japan took into account, patients treated with Supraclavicular, mediastinal and celiac regions in both younger and older patients. The study reported that there was about 29% risk of cardiopulmonary toxicities in older (>75 years) patients compared to only 3% in younger patients. Hence, the study concluded, that older patients may not tolerate extensive

radiation fields, and hence the treatment fields should be tailored according to each individual. Other studies (19) also reported that there was significant decline in diffusion capacity and total lung volume in patients treated with irradiation for esophageal cancer.

In a study from MD Anderson Cancer Center (20) , 110 patients were treated with preoperative chemoradiation, and the mean lung dose, effective dose and absolute lung dose receiving less than or equal to 5Gy were calculated which proved to predict the risk of developing postoperative pulmonary complications. In this, 18% developed pulmonary complications, with higher rates when the V10 values were more than or equal to 40% (35% vs 8%) and V15 values of more than or equal to 30% (33% vs 11%). The authors concluded that minimization of irradiated lung volumes led to reduced postoperative pulmonary complications. This increase in postoperative pulmonary complications like pneumonitis, acute respiratory distress syndrome, when V10 value was more than 40% suggest that volume of remaining or undamaged lung tissue may predict postoperative pulmonary complications. In other words, patients with smaller lung volume to begin with will experience higher rates of postoperative pulmonary complications. Also patients with less functional reserve may be more susceptible to postoperative pulmonary complications. Hence, it is essential to calculate total lung volume in addition to dose volume histogram.

A Chinese study (21) evaluated patients receiving chemoradiotherapy followed by resection showed that volume of lung sparing more than or equal 5 Gy was the only predictive independent dosimetric factor in analyzing postoperative pulmonary complications. Wang et al described that the relative V5 of all volumes spared from 5 Gy to 35 Gy correlated significantly with the incidence of postoperative pulmonary complications, although on multivariate analyses, V5 proved to be the only significant predictive prognostic factor, indicating that the volume of unexposed lung during induction therapy was predictive. The majority of patients in this study were treated with induction chemotherapy, mostly paclitaxel, which had shown to increase the rate of pneumonitis in other sites. A significant association of induction chemotherapy prior to concurrent chemoradiotherapy was found to be a predictive factor for Grade 2 or greater pneumonitis (48% vs 13% respectively). Hence, it concluded that, induction chemotherapy alone will sensitize lung tissue to radiation damage. Compared to this, another study evaluated 98 patients, who received preoperative chemoradiotherapy with 5-FU and cisplatin followed by surgery had no significant postoperative pulmonary complications leading to the conclusion that neoadjuvant chemoradiation had no detrimental effect in lung toxicity. Finally, a Taiwanese study (23) using IMRT in esophageal cancer evaluated the preoperative forced expiratory volume in one second (FEV1) and showed that it was a significant independent predictive factor, and that reducing

the absolute dose to the right lung might reduce the incidence of significant postoperative pulmonary complications.

Radiation induced cardiac toxicity:

Radiation induced cardiac toxicity involves injury to numerous structures like pericardium, which manifests as effusion or pericarditis, coronary arteries, heart muscle fibres, cardiac valves, or nerve and conduction defects. Radiation mainly leads to fibrosis or small vessel injury. Classic radiation tolerance values i.e TD 5/5 for the heart is about 60 Gy when the irradiated volume is less than or equal to 25%. Similarly, TD 5/5 is 45 Gy when the irradiated volume is about 65%. The mechanism that leads to cardiac injury especially in esophageal cancer is poorly defined. Historically, treated patients with Hodgkin's disease who received more than 40 Gy led to increased cardiac morbidity and mortality. Roughly, V30 of more than 46% predicts an increased risk of having pericardial effusion leading to increased cardiac morbidity. Also, there was reports stating that increased V20 dose to left ventricle led to decrease in ejection fraction, and thereby functioning of the heart.

Pulmonary function testing:

Pulmonary function test (PFT) is a complete battery of tests that involves patient history, Clinical examination, Chest X-ray, Arterial Blood gas analysis

and tests of pulmonary function. It is done mainly to assess the functional integrity of lungs and to understand the severity of pulmonary function impairment. It has both diagnostic and therapeutic roles and usually done by a separate technician.

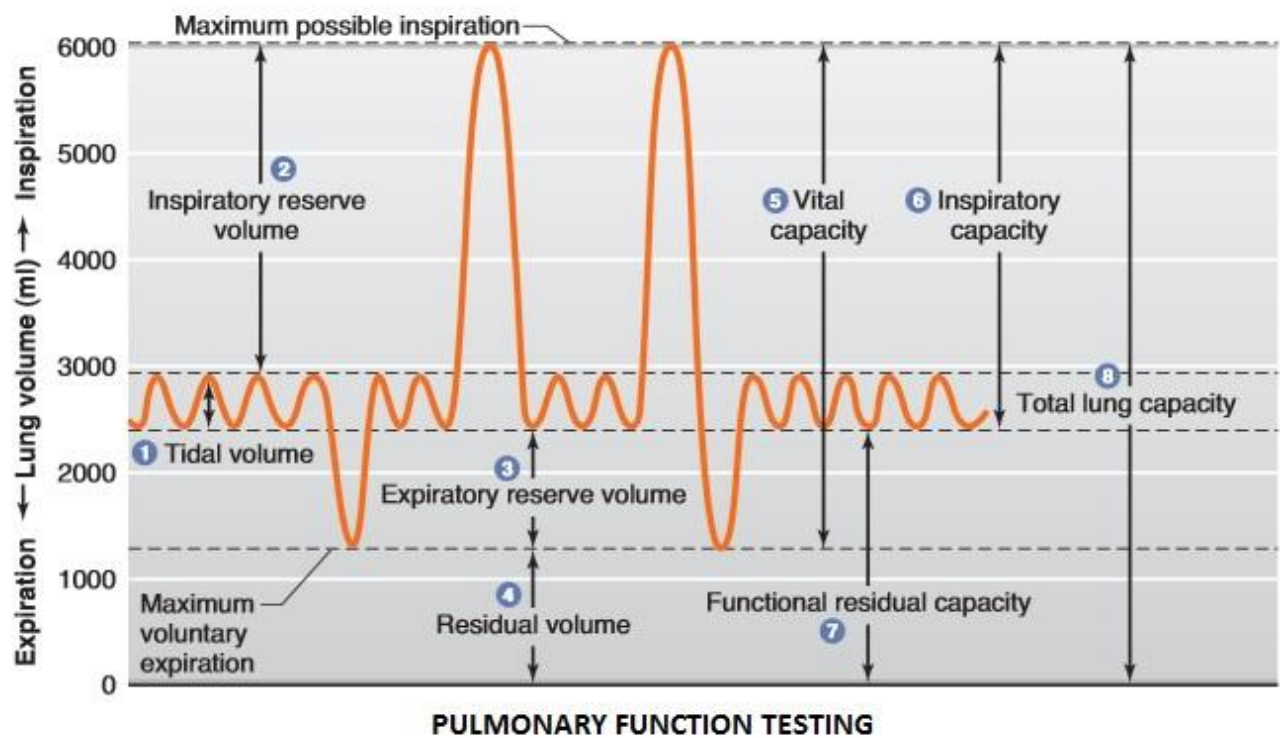
Lung volumes:

Lung volumes (23) and lung capacities are associated with different phases of respiratory cycle. Lung volumes are directly calculated, and lung capacities are inferred from the same. The average lung capacity for an adult male is about 6 litres of air. Among this, only a few percentage is used for normal breathing. The average respiratory rate is about 30-60 breaths per minute at birth, reducing to around 12-20 in adult. Some of the lung volumes that are measured are:

- Total lung capacity (TLC): This is the measured volume of lungs at maximal inflation, this is the sum of both residual volumes and vital capacity.
- Tidal volume(TV) is the volume of air that moves in and out during quiet breathing.
- Residual volume (RV) is the volume of air that remains after a maximal expiration.
- Expiratory reserve volume (ERV) is the volume of air that can be exhaled from end expiratory position.

- Inspiratory Reserve volume (IRV) is maximal volume of air that can be inhaled from end inspiratory level.
- Inspiratory capacity (IC) is the sum of inspiratory reserve volume and tidal volume.
- Vital capacity (VC) is the volume of air exhaled after maximum inspiration.
- Inspiratory vital capacity (IVC) is the maximum volume of air inhaled after maximum expiration.
- Functional residual capacity (FRC) is the volume of lungs at end expiratory position.
- Forced vital capacity (FVC) is the vital capacity that is measured after a maximal forced expiratory effort.
- Forced expiratory volume (FEV1) is the volume of air exhaled at the first second of forced expiration.

Type	Examples	Volumes	FEV1/FVC
Restrictive	Interstitial lung disease	Volumes are decreased	In normal range (0.8-1.0)
Obstructive	COPD, Asthma	Volumes are normal but flow rates decreased	Reduced (<0.8)

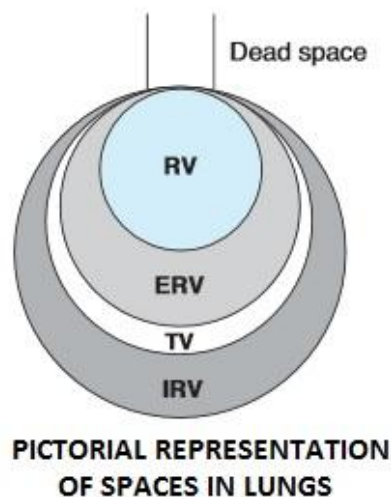


Indications for Pulmonary Function Testing:

- Neuromuscular disorders like Duchenne Muscular dystrophy
- Chronic dyspnea
- Asthma
- Preoperative testing
- COPD
- Restrictive lung diseases
- Disability or functional impairment

Spirometry:

Spirometry measures Forced vital capacity, Forced expiratory volume FEV1, Forced inspiratory flow rates, etc. By measuring these volumes, spirometry assess the ability of lungs to move air in and out through the airways to identify any airway obstruction or restriction.



By spirometry, a pneumotachograph is obtained, with which lung conditions like cystic fibrosis, asthma, COPD, pulmonary fibrosis, interstitial lung diseases etc can be identified. It may be also used for diagnosing bronchial hyperresponsiveness to cold air, exercise or drugs.

Complications of spirometry include syncope, chest pain, paroxysmal cough, pneumothorax, nosocomial infections, increased intracranial pressure, oxygen desaturation and bronchospasm.

3.ORIGIN OF THE STUDY:

Our institute records about 350 esophageal cancers per year; among which only 50% of the cases are treated due to various factors. Most of the esophageal cancers present with advanced stage at diagnosis. The treatment modality includes either definitive chemoradiation; neoadjuvant chemoradiation followed by surgery or Surgery followed by postoperative adjuvant chemoradiation. As esophagus is a thoracic and abdominal structure, many of the vital structures come into the field of radiation, and hence, in this modern era of radiation oncology, using sophisticated techniques like the conformal or IMRT have become the modality of choice to deliver radiation, so that, treatment is planned by avoiding dose to the surrounding normal tissues. On such contexts, delivering techniques like IMRT will not be feasible in all places, due to costs and other factors. In places like our institute, where number of patients treated per day per machine is high, treating all patients with IMRT will not be an ideal strategy. Also, due to the high integral dose in IMRT, low dose irradiation to normal tissues might pose a significant health hazard, along with the fact, long term data for IMRT is not available. Hence, the concept of Hybrid conformal technique arose, where tumours can be treated with a better intent of reducing the integral dose, time taken for treatment, without compromising on the dose distribution.

4.AIM OF THE STUDY:

To assess the feasibility of Hybrid conformal technique in treatment of Esophageal cancers thereby achieving a non inferior dose distribution to that of IMRT, to reduce the volume of lung treated, and also to calculate the time taken for both.

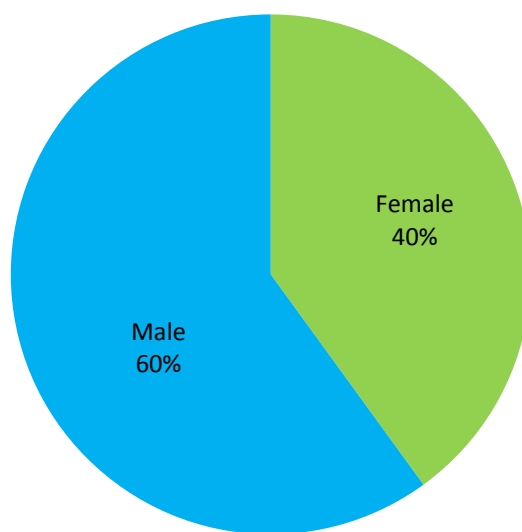
5.MATERIALS AND METHODS:

Patients:

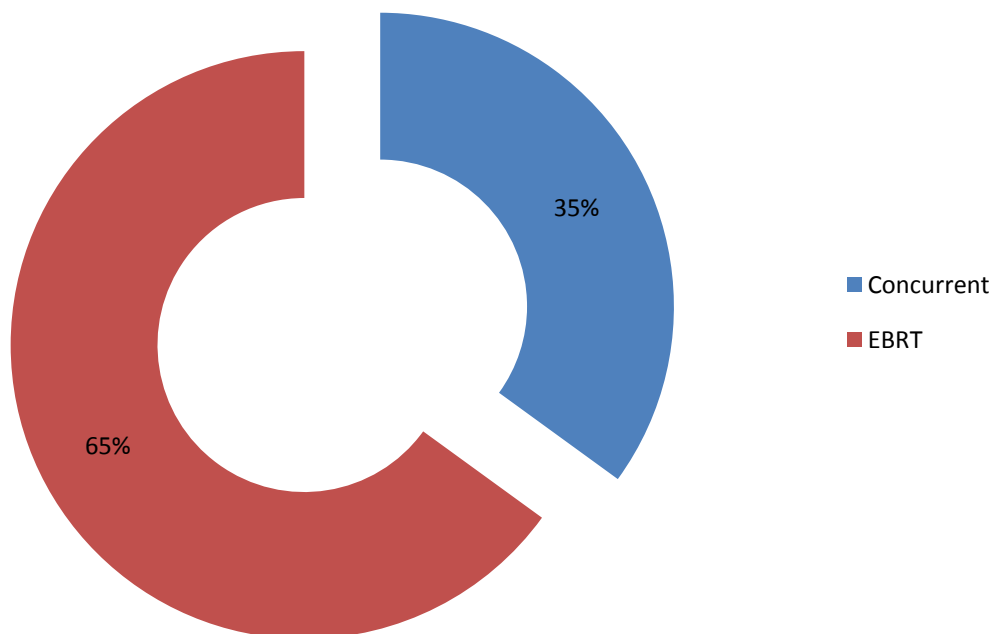
Twenty patients were considered for this prospective study. Patients were planned for both Hybrid conformal and IMRT techniques from the year December 2013 to September 2014 and their dose volume histograms were calculated. Patient characteristics are as given in the following table.

Gender (Male : Female)	12:8
Dose	54Gy
Chemotherapy	7 patients
Total lung volume	3800cc
Ipsilateral lung volume	2000cc
Contralateral lung volume	1800cc

Gender



Chemoradiation and Radiation



Inclusion Criteria:

1. Age 35-75 years
2. Both Sexes
3. Histology-Squamous cell carcinoma
4. Carcinomas of thoracic Esophagus
5. Concurrent Chemotherapy
6. Radiation Therapy alone
7. ECOG Performance status 0,1 and 2.
8. Patient who do not have metastatic disease
9. Patients with adequate bone marrow function defined as Absolute peripheral Granulocyte count of >2000 cells/mm³; platelet count of >100000 cells/mm³; adequate hepatic function with Serum Bilirubin <1.5 mg/dl; Serum Creatinine <1.5 mg/dl;creatinine clearance of >50 ml/min; SGOT or SGPT <2 x the normal; and normal Serum Calcium.

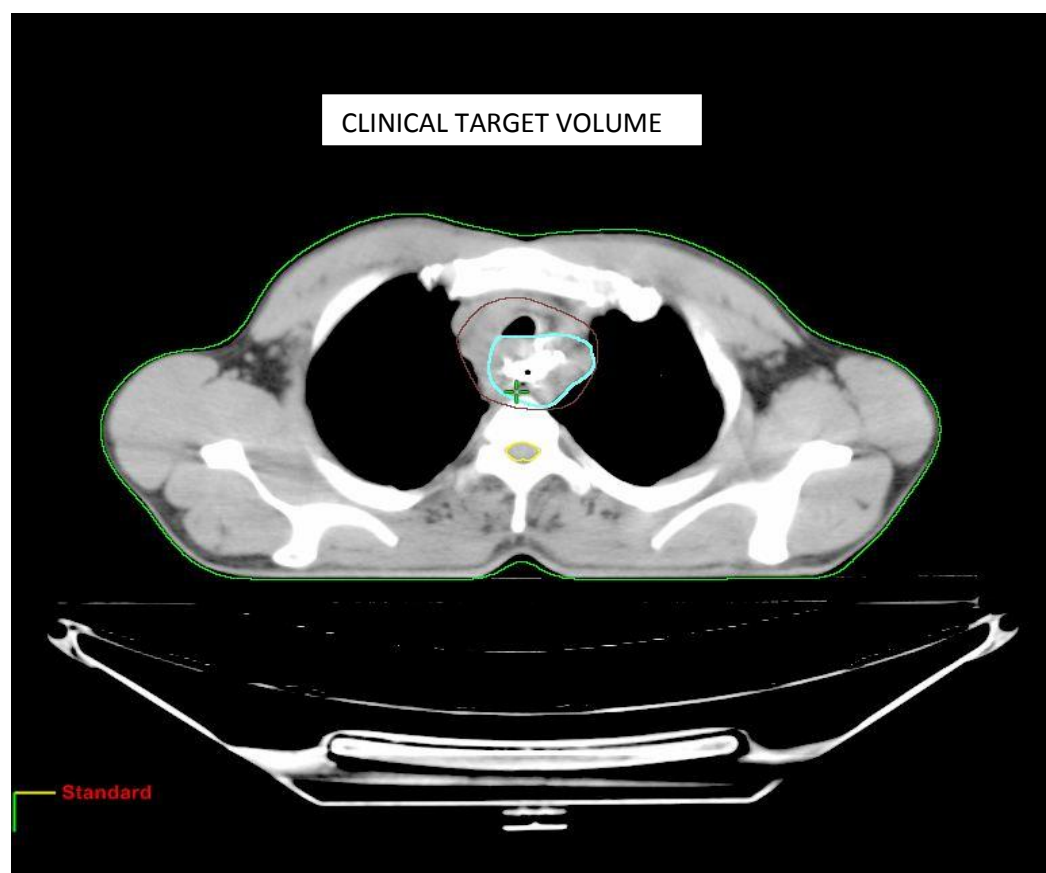
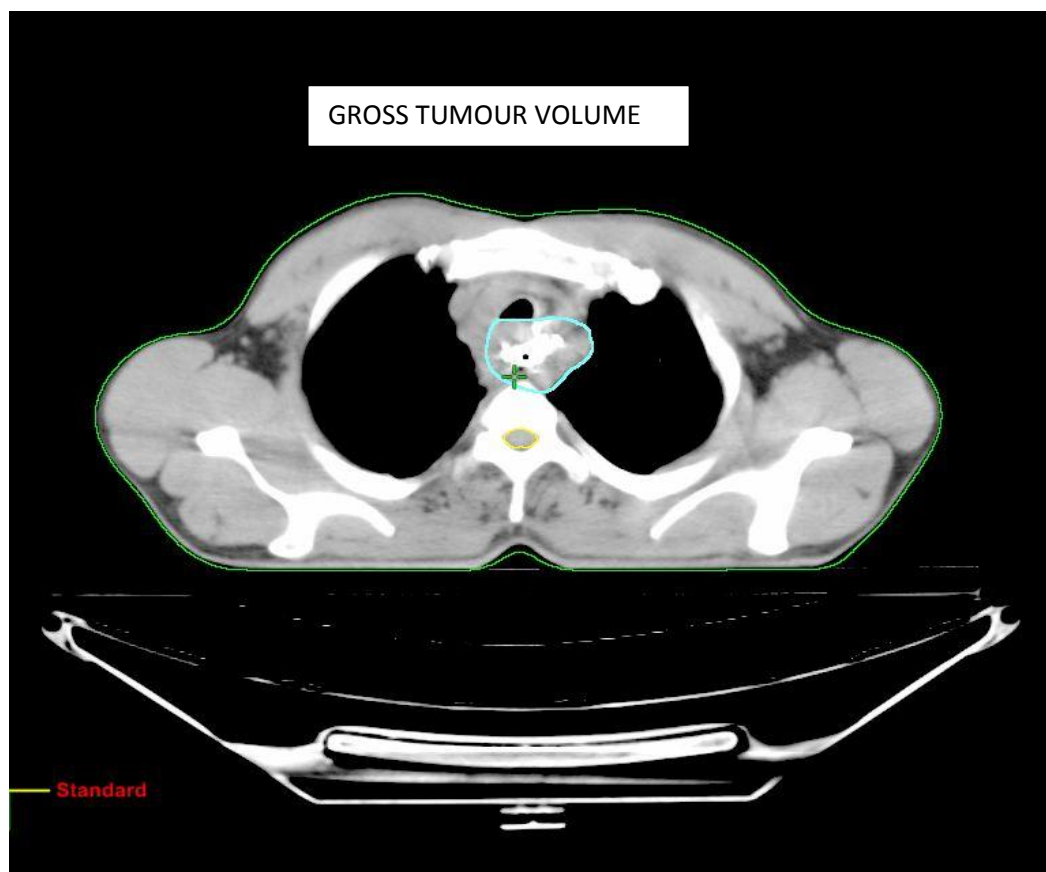
Exclusion Criteria:

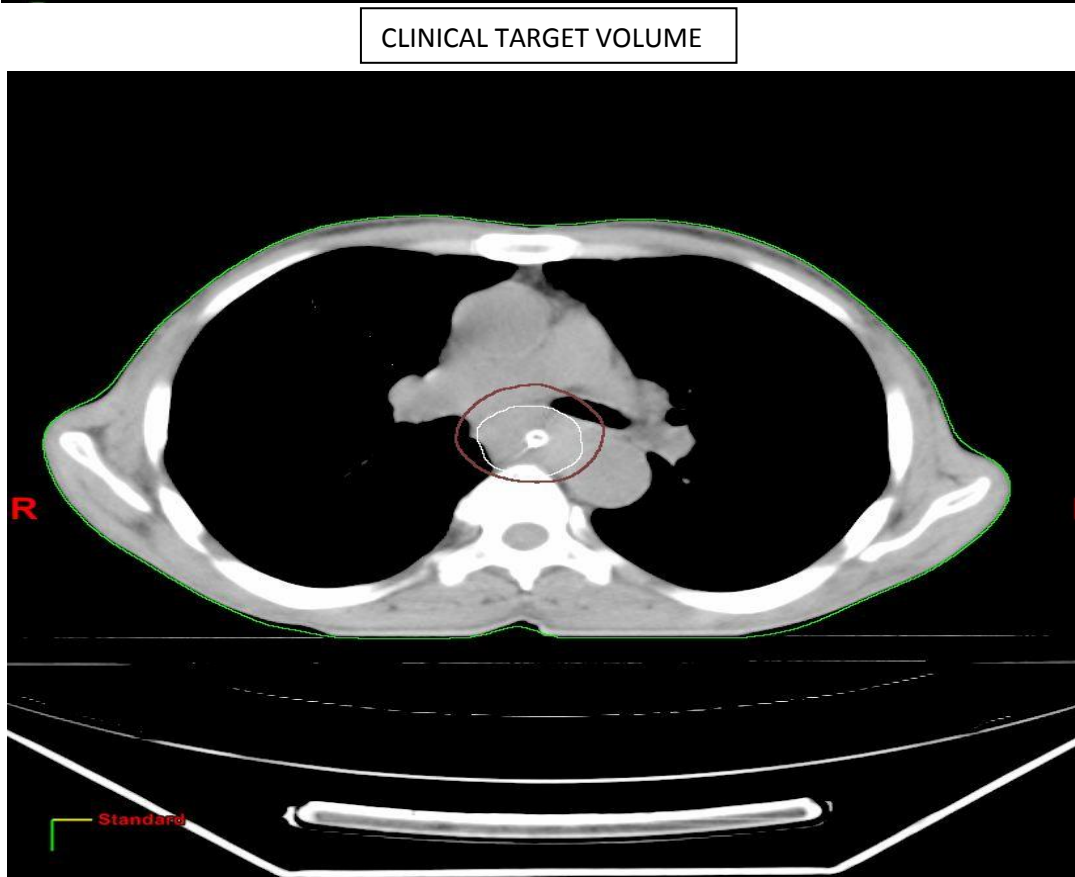
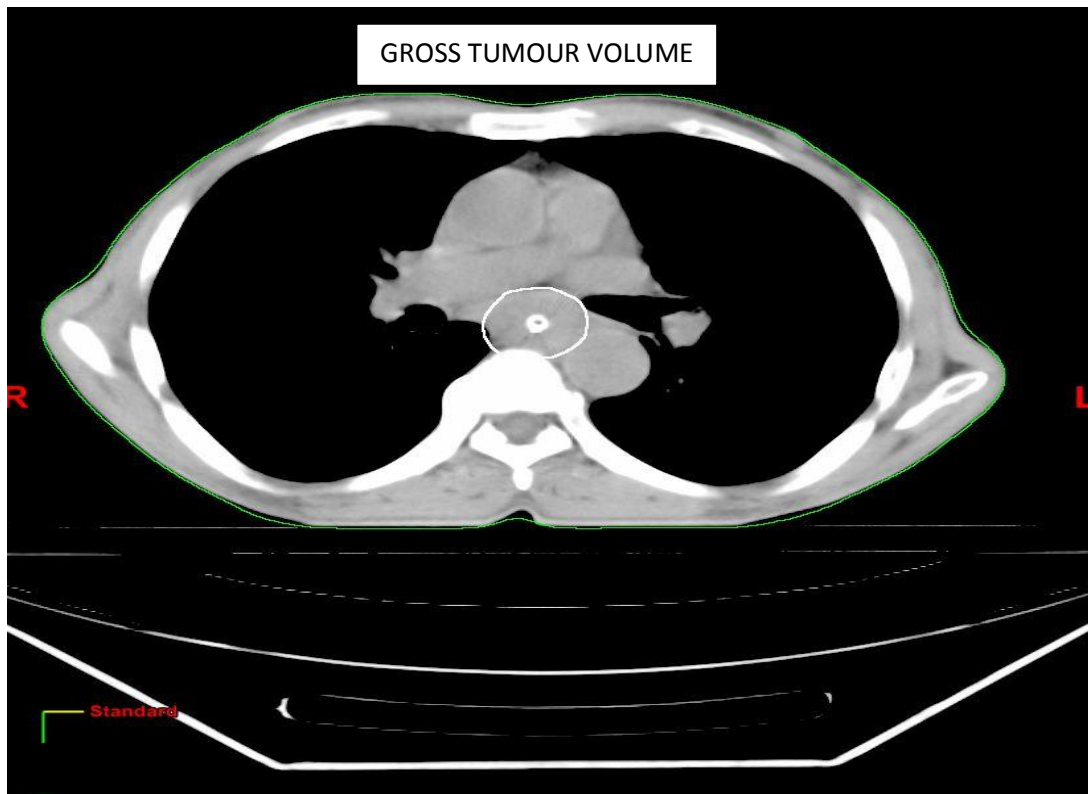
1. Patients with prior irradiation to Chest
2. Histology-Non Squamous cell carcinoma

3. Carcinoma of Cervical Esophagus and involving OG junction.
4. Age<35 and >75 years
5. Metastatic Carcinoma Esophagus
6. Patients with bone marrow suppression, abnormal renal and liver function tests, Creatinine clearance of <50ml/min; and low serum calcium.
7. Patients with ischemic heart disease or myocardial infarction.
8. Pregnant women.
9. Patients with simultaneous primaries.

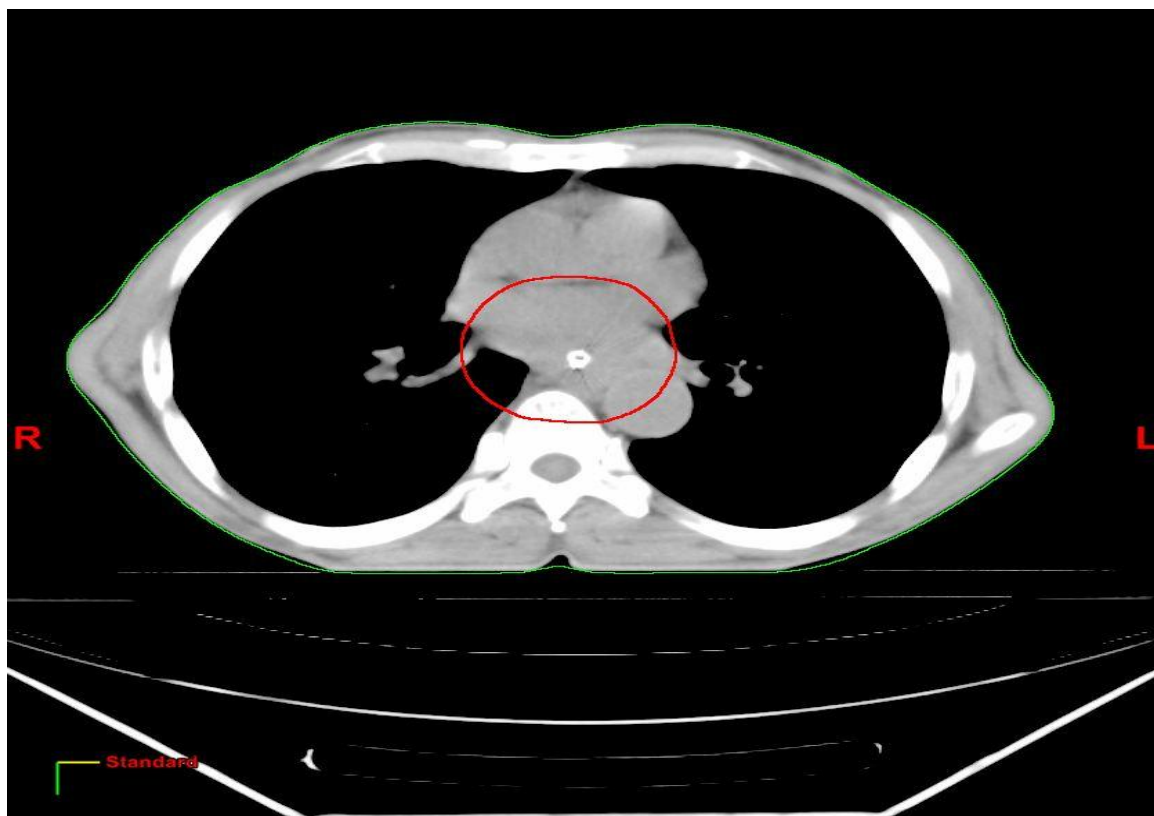
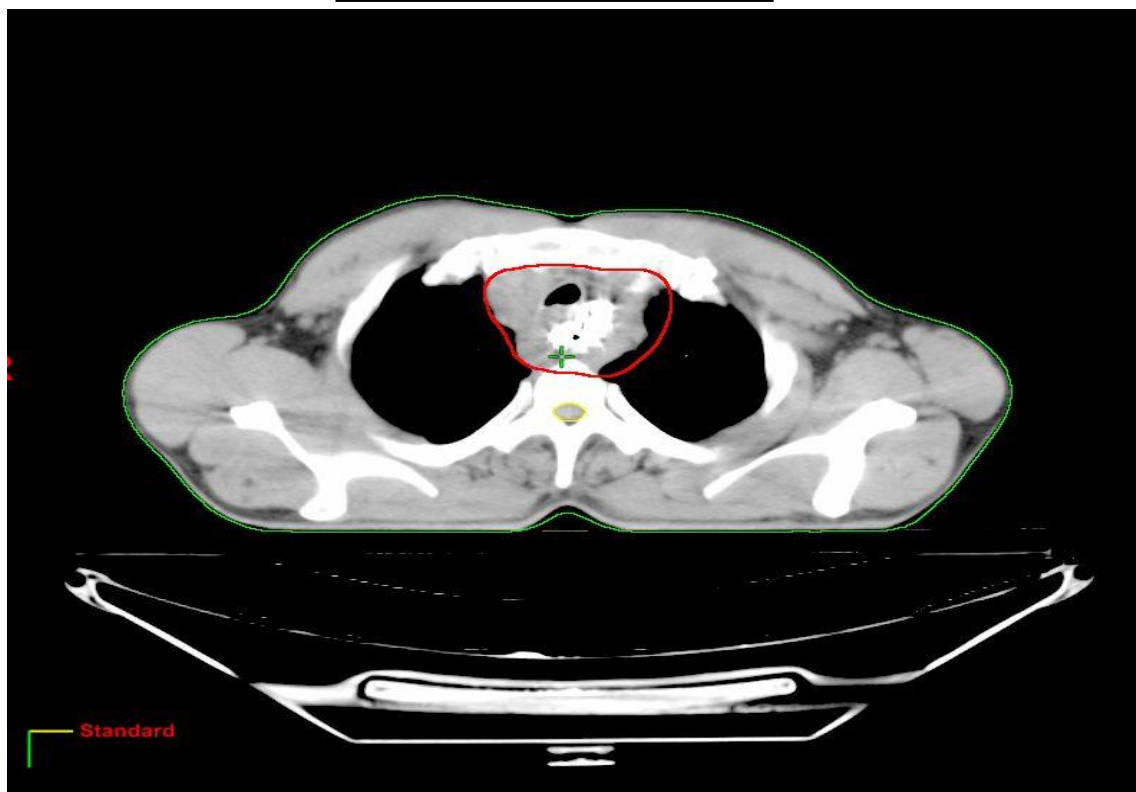
Contouring:

All patients underwent CT scans with 5mm slices during normal breathing. No specific measures were taken to control respiratory movements. This was subsequently followed by delineating the gross tumour volume, for which Clinical target volume was made. Furthermore, Planning Target volume (PTV) were drawn with a superior and inferior margin of 5cm and radial margin of 2-2.5cm were done. The spinal cord, heart, left and right lungs were contoured. Patients also underwent Pulmonary function testing before start of the treatment, so that basic functioning of lungs can be assessed and compared at the end of treatment.





PLANNING TARGET VOLUME

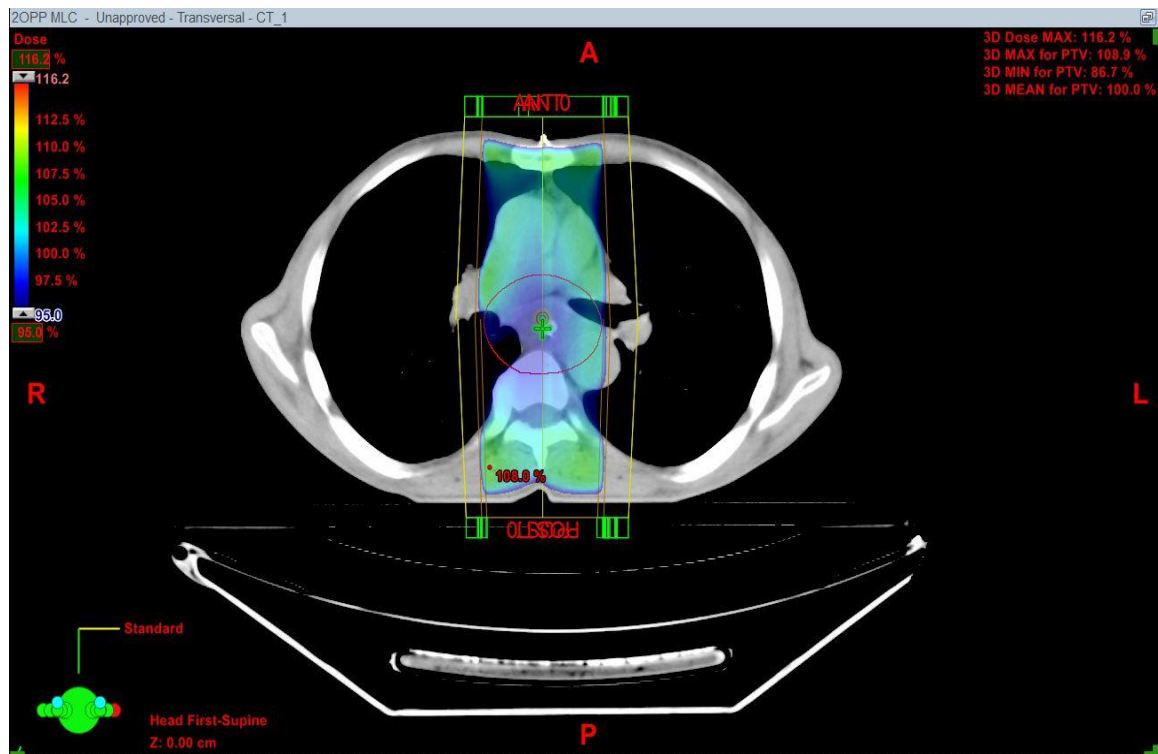
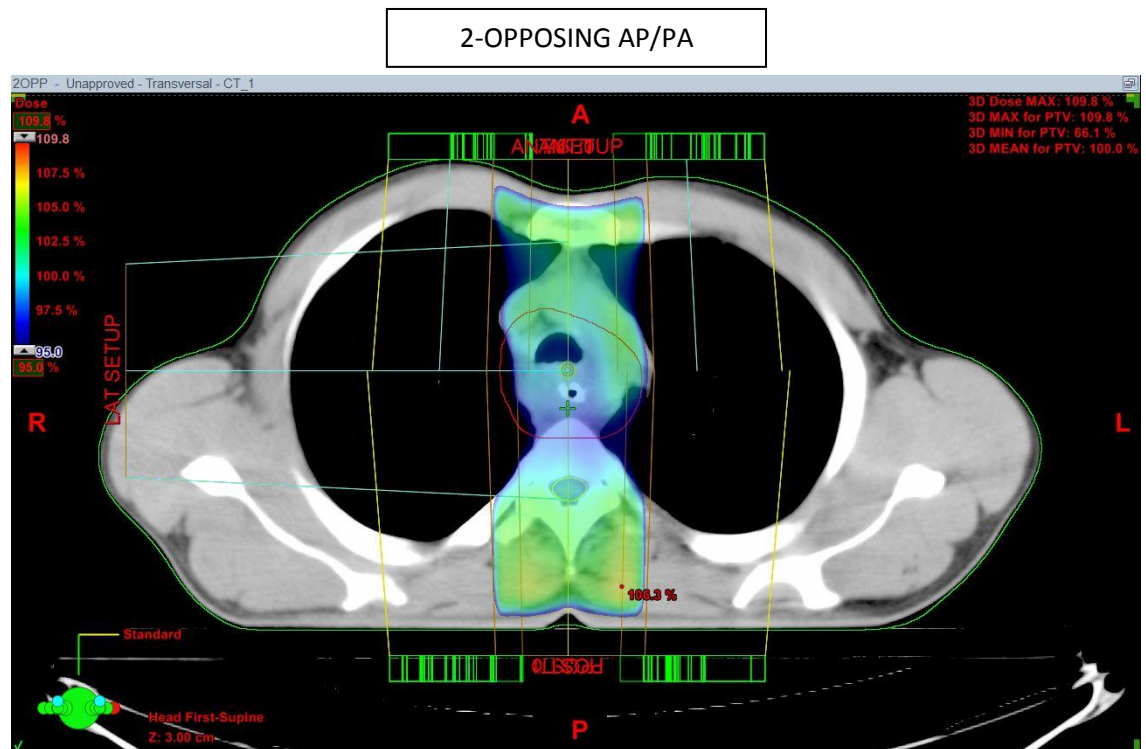


Dose Prescription and Planning technique:

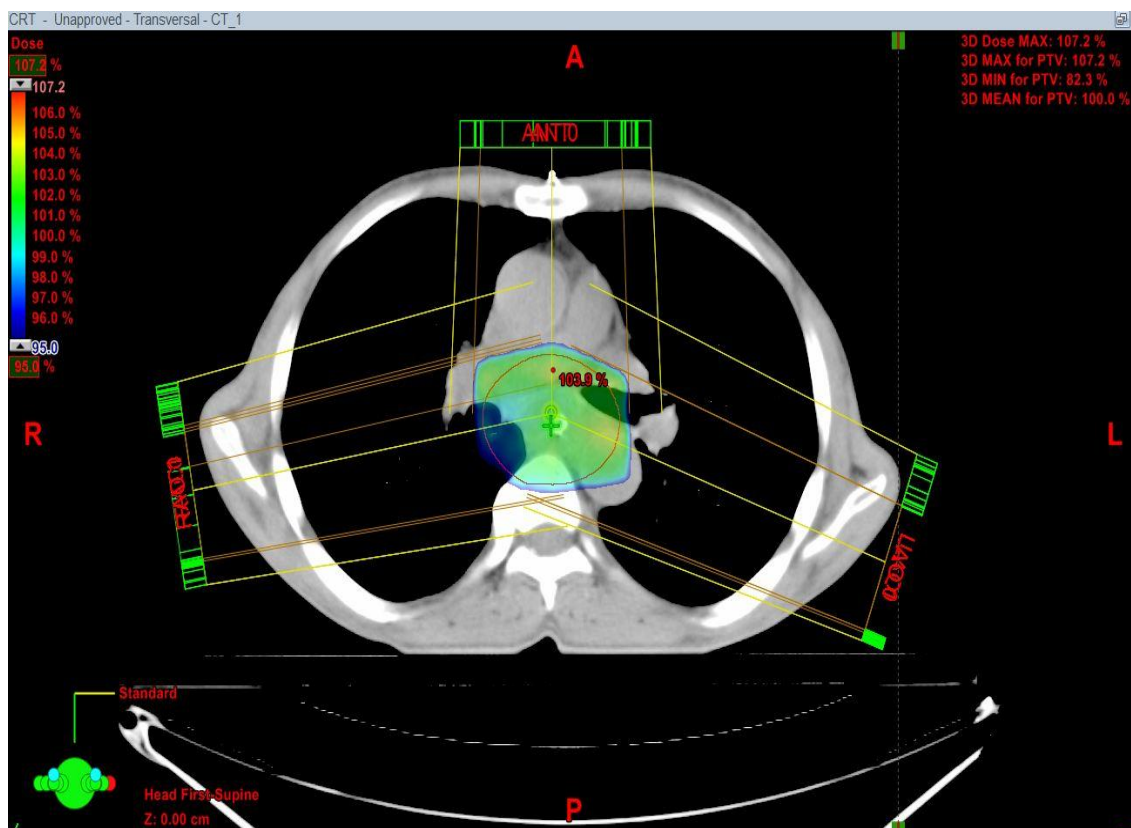
Treatment planning was done with the help of Varian treatment planning systems. Dose calculations were done with the help of Analytical Anisotropic Algorithm(AAA). Then planning was done for both hybrid conformal and IMRT techniques. Hybrid conformal technique consists of static beams that delivers half the dose of radiation with the help of two opposing Anteroposterior-Posteroanterior fields, followed by conformal technique which delivers the remaining dose. Approximately, the two opposing fields were given upto a total dose of 30 Gy followed by conformal technique which delivers the remaining 24 Gy with the same PTV thereby totalling to a dose of about 54 Gy. Literature reviews indicate a treatment dose of about 50-50.4 Gy. But based on our Institute protocol, treatment were delivered to a total dose of 54 Gy. Daily doses were given with 200cGy per fraction per day.

Anteroposterior and posteroanterior fields, as the name suggests, were treated with two opposing fields, followed by conformal technique. Conformal technique were delivered with the help of four field technique, with minimization of lung volumes. Comparing to this, an all-IMRT plan was made with the help of seven to eight fields, thereby achieving the target volume, minimizing the doses to normal tissues. IMRT beams were oriented in such a

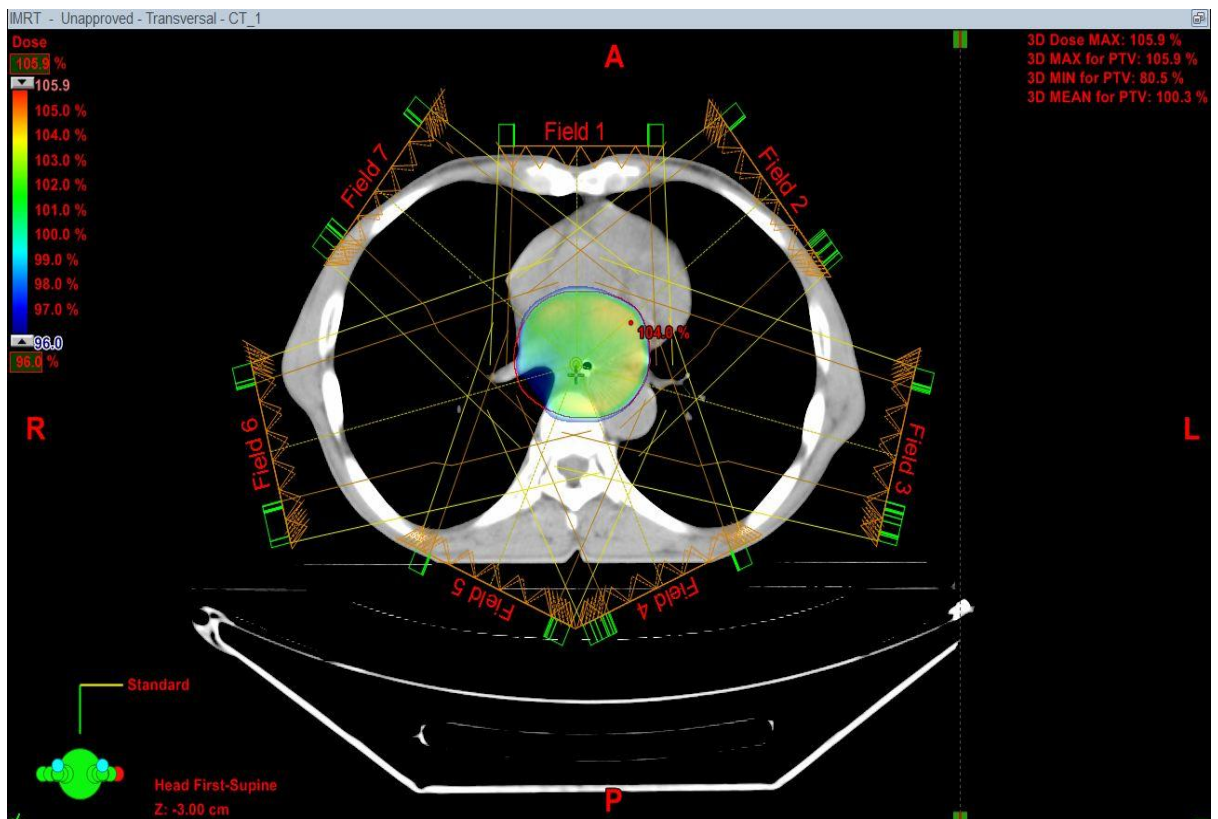
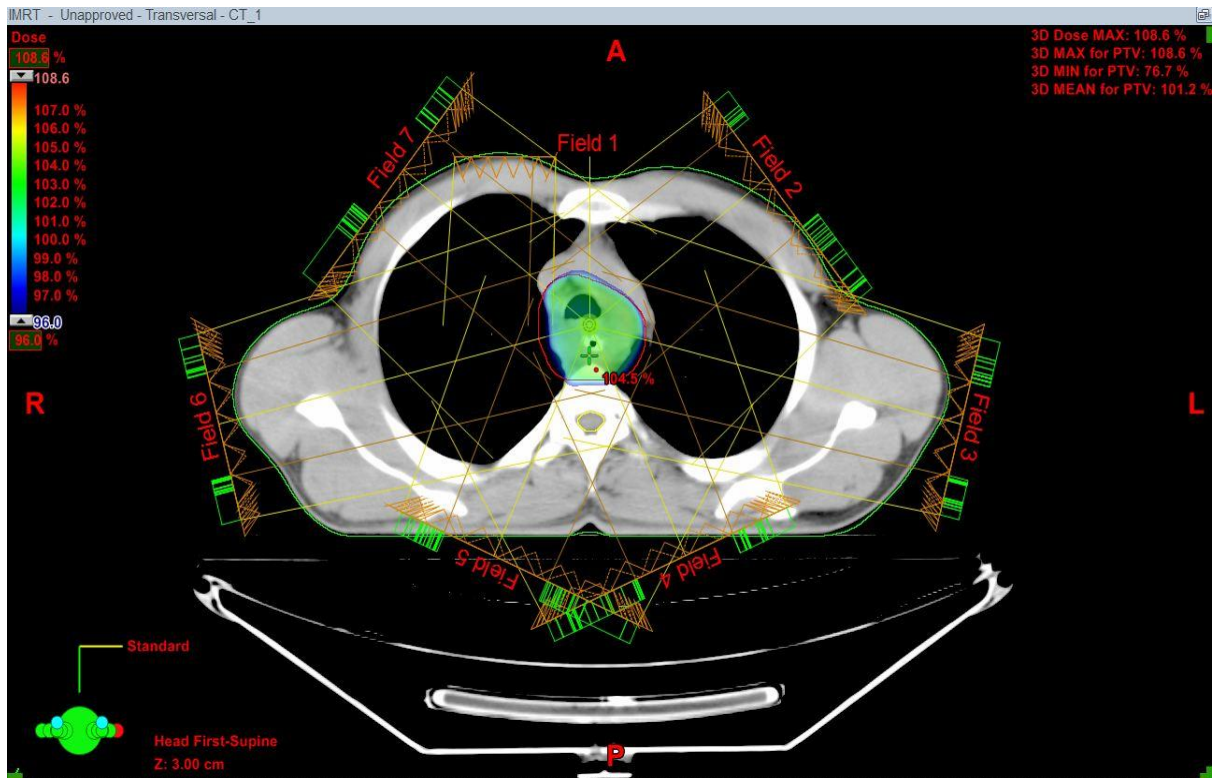
way that the beams are non opposed and at different angles, thereby avoiding the spinal cord. It is illustrated below.



CONFORMAL TECHNIQUE WITH THREE OF FOUR FIELDS



IMRT



Dose volume histograms are then calculated for both the planning target volume (PTV) and organ at risk. The MLD, volume of lung receiving 20 Gy (V20) for both lungs and mean dose to heart are calculated. It is compared with Hybrid Conformal technique and assessed. V30 for heart is also noted.

Patients then are treated with two opposing anteroposterior and posteroanterior fields, upto a total dose of 30 Gy followed by conformal technique upto a TD of 54 Gy. Those patients who receive concurrent chemotherapy are treated with three weekly cisplatin with a dose of 70mg/m² or weekly cisplatin with a dose of 40mg/m². Patients are carefully noted for side effects of radiation like esophagitis, mucositis, pneumonitis, chest pain, dyspnea or bone marrow suppression. After completion of treatment, patients again are subjected to pulmonary function testing and compared with the initial values.

Patient Outcomes:

Patients are advised to review after six weeks initially and then followed up at monthly intervals.

6.RESULTS:

Patient characteristics:

Among the twenty patients treated, twelve patients were males and eight patients were females. Out of them, twelve patients were carcinomas of middle thoracic esophagus, six involve upper thoracic esophagus and two belong to lower thoracic esophagus without involving gastroesophageal junction. All these patients underwent Hybrid conformal technique and were also planned for all-IMRT plans. Patients also underwent pulmonary function testing both before and after treatment. Among the twenty patients, thirteen patients are treated only with radiation therapy and seven patients received concurrent chemoradiation. Out of the chemotherapy patients, four patients received three weekly cisplatin and three patients received weekly cisplatin due to their biological tolerance.

Dose volume histogram of these twenty patients were analyzed extensively and found that dose distribution attained by Hybrid conformal technique was not at all inferior when compared to that of IMRT plans. IMRT, being a modern superior technique achieved a uniform dose distribution for all these patients, confined to the planning target volume. On the other hand, in Hybrid conformal technique, dose distribution achieved in planning target

volume was not inferior to that of IMRT plans, achieving the same dose without compromising the tumour volume.

There was no incidence of pneumonitis in any of these patients. The V20 calculated were less than 30% in all these patients. The lung dose was calculated by taking into account the combination of both right and left lungs. Both Hybrid conformal and IMRT plans were able to achieve a V20 value of less than 30%. Also, the mean lung dose for both Hybrid conformal and IMRT techniques were less than 20 Gy. But noting the difference in both these techniques, Hybrid conformal technique achieved a much lesser lung dose compared to the all-IMRT plan in both V20 as well as mean lung dose. It showed that both V20 and mean lung dose achieved in Hybrid conformal technique was atleast 5% lesser in V20, and atleast 1 to 2 Gy lesser than IMRT plans.

No of Patients	V20 Hybrid conformal(%)	V20 IMRT(%)
1	16.52	18.66
2	12.22	19.95
3	13.32	22.78
4	16.03	22.98
5	12.46	15.71

6	12.81	17.67
7	15.93	24.50
8	10.26	22.33
9	17.88	19.88
10	16.86	18.73
11	15.77	18.42
12	16.12	19.18
13	15.87	18.06
14	12.12	16.55
15	14.66	19.14
16	16.97	20.81
17	13.86	18.88
18	16.11	20.08
19	14.76	19.66
20	13.12	17.84

No of Patients	MLD Hybrid conformal(Gy)	MLD IMRT (Gy)
1	15.18	16.42

2	12.31	14.67
3	10.98	14.48
4	11.93	16.05
5	10.73	11.48
6	11.55	17.55
7	15.10	18.08
8	11.85	14.44
9	16.83	18.01
10	14.22	15.42
11	11.88	13.88
12	14.12	16.56
13	13.88	16.68
14	10.04	13.88
15	12.81	16.14
16	13.16	14.22
17	11.88	16.56
18	14.06	18.51
19	12.64	17.81
20	12.08	15.67

The cord dose achieved in IMRT is much lesser than than the usual constraint of 45Gy point dose. Similarly, the cord dose achieved in Hybrid conformal technique was much higher than that of IMRT, but still being achieved with in a dose of 45Gy.

No of Patients	Cord dose Hybrid conformal(Gy)	Cord dose IMRT (Gy)
1	44.98	41.16
2	44.48	40.20
3	44.72	40.35
4	43.77	42.79
5	44..32	41.87
6	44.55	40.88
7	44.37	41.86
8	45.01	42.60
9	44.67	40.45
10	43.89	40.04
11	43.98	40.01
12	44.95	41.11
13	44.86	39.96

14	43.86	41.01
15	44.44	40.90
16	43.98	42.22
17	45.04	43.97
18	44.87	40.05
19	43.78	41.87
20	43.98	42.05

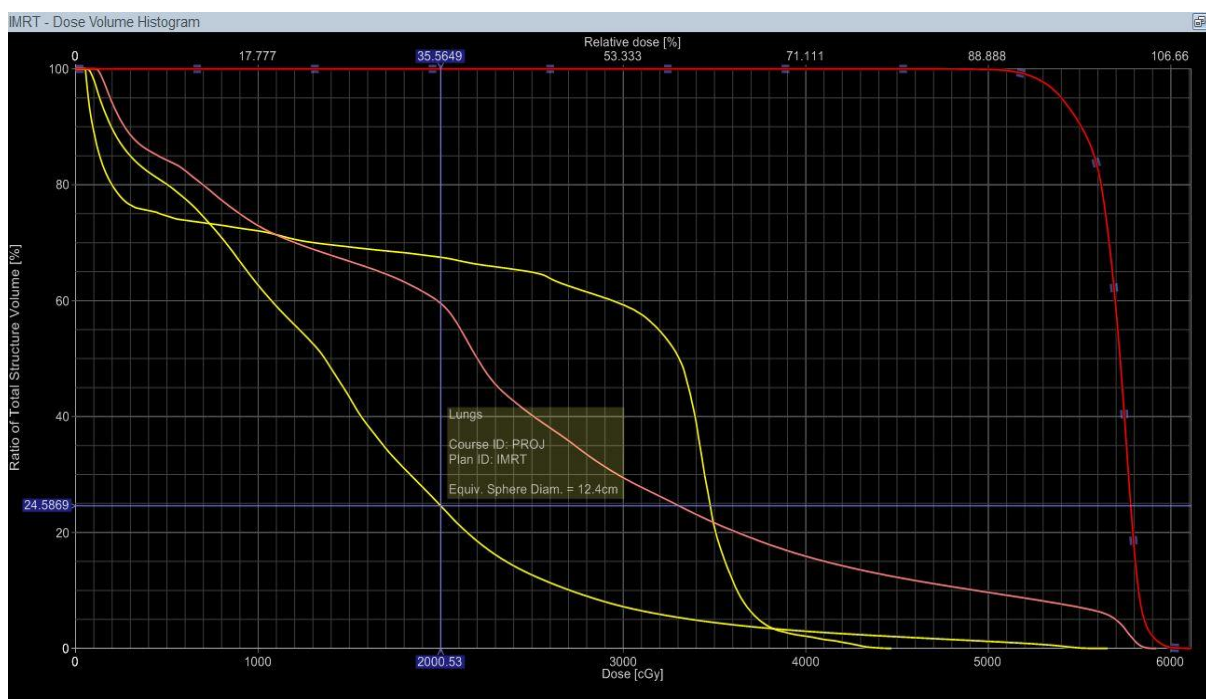
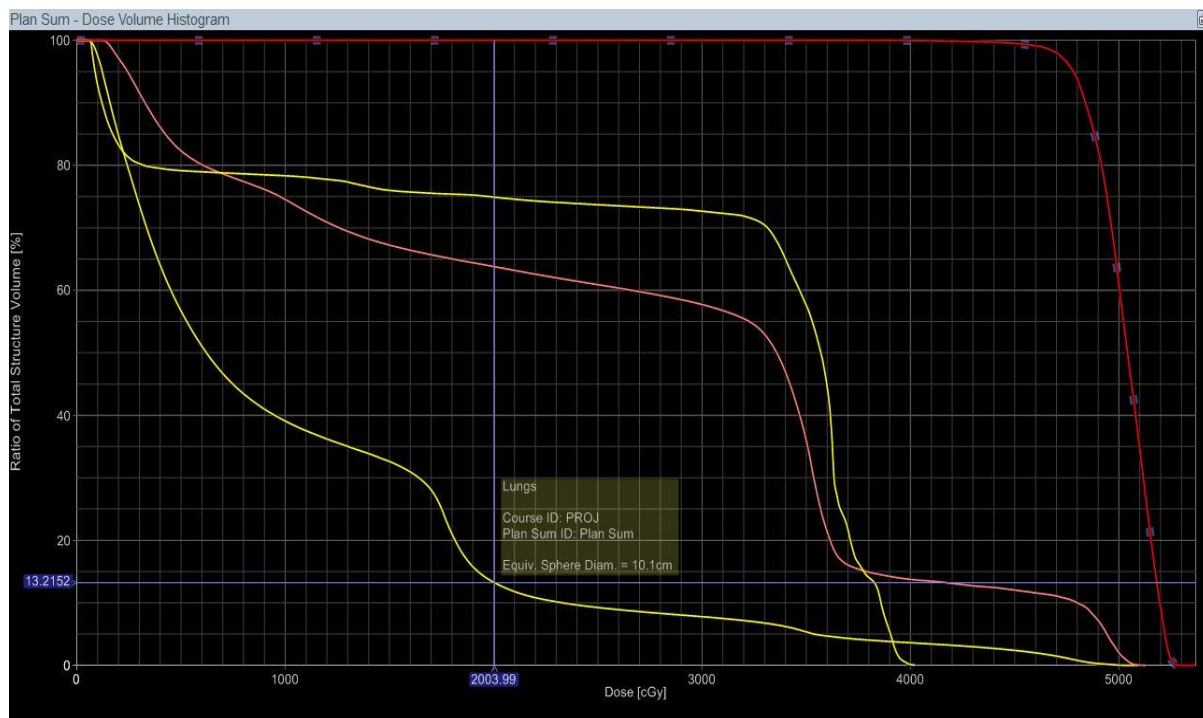
The other main organ at risk in the treatment field is heart, which usually is in the plane of treatment. The mean dose to heart for these twenty patients under study were less than 30 Gy. The V30 calculated for the heart is less than the usual constraint of 46Gy.

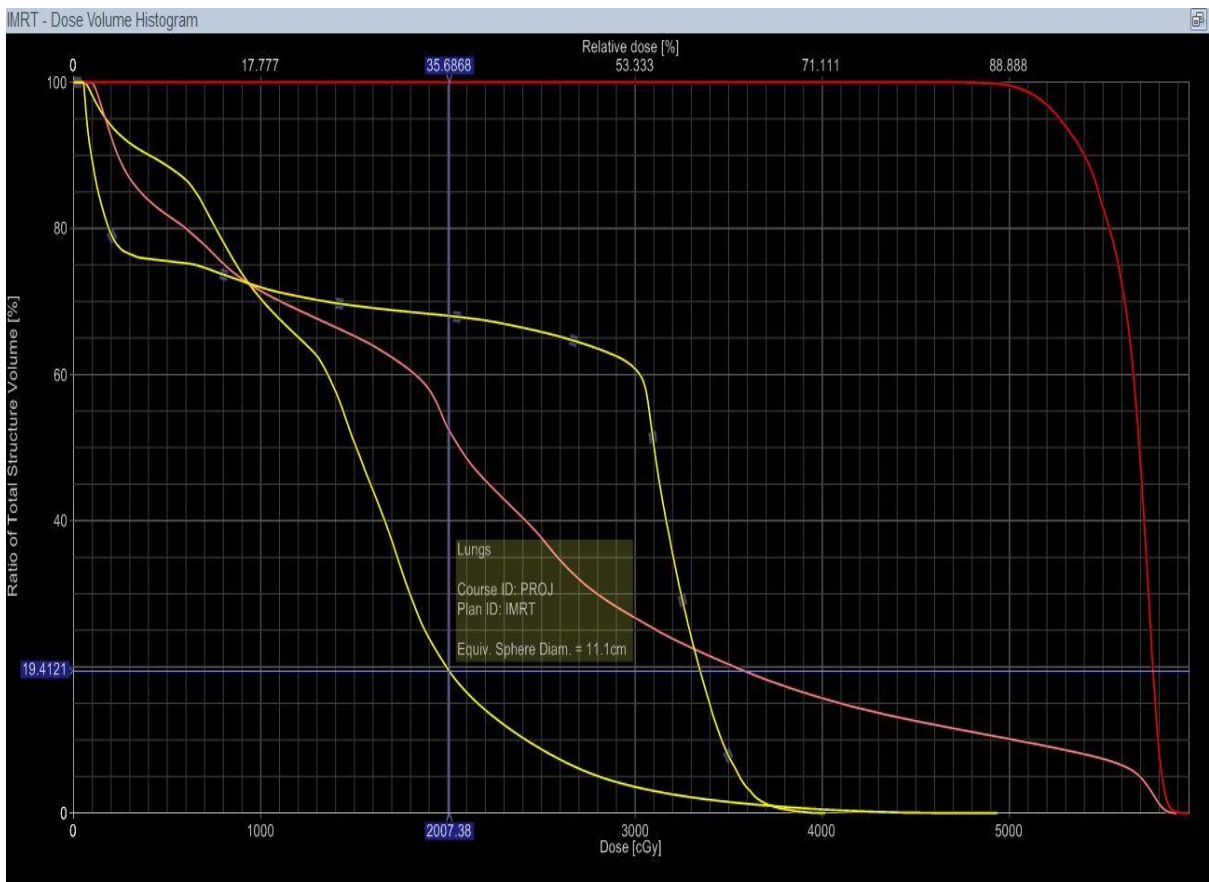
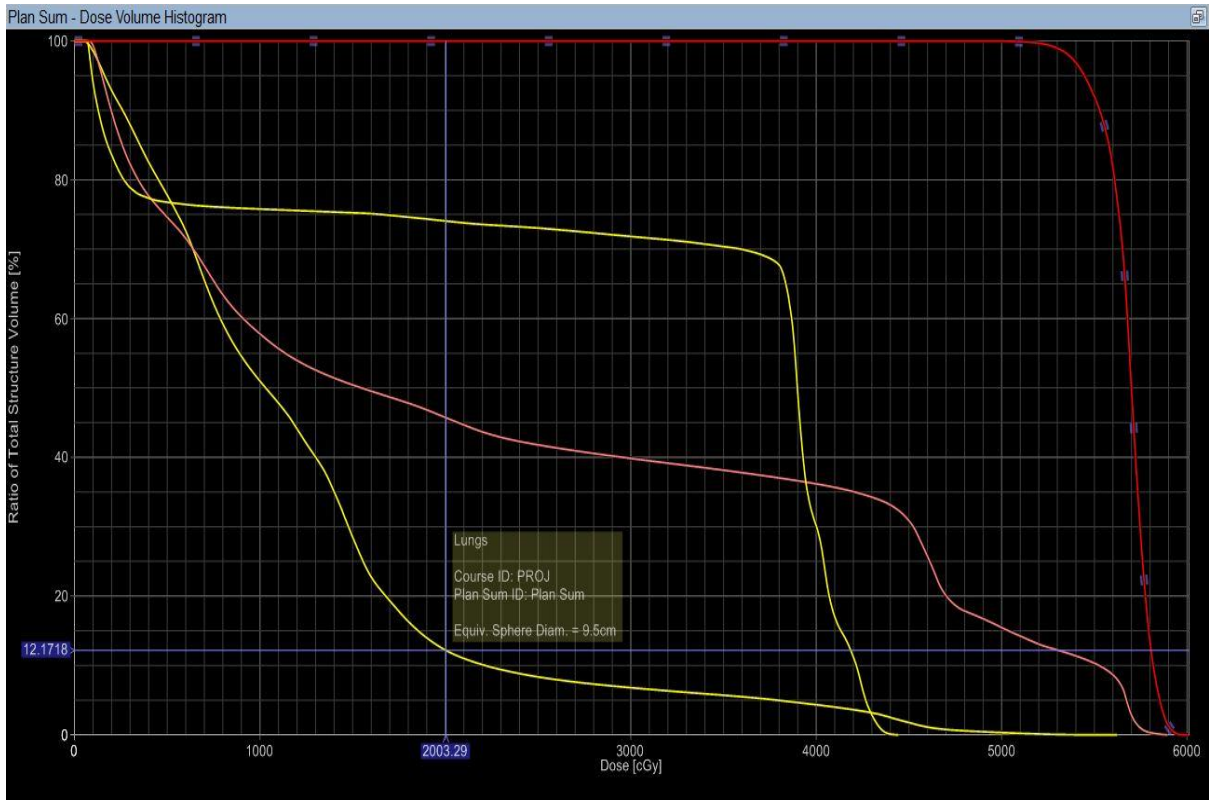
No of Patients	Heart mean dose Hybrid conformal (Gy)	Heart mean dose IMRT (Gy)
1	30.87	28.25
2	24.32	26.55
3	26.07	24.03
4	25.36	24.22
5	20.21	18.88
6	23.85	21.91
7	29.82	27.25

8	29.91	27.71
9	30.44	28.61
10	26.88	24.14
11	28.88	25.82
12	29.76	28.85
13	26.82	25.96
14	27.68	26.52
15	29.86	27.98
16	23.67	22.86
17	25.52	24.42
18	26.87	25.76
19	27.12	26.01
20	28.84	26.04

Pulmonary function testing was done both before and after treatment. The twenty patients under consideration had no abnormal deviation of pulmonary function testing, except for one patient, who had restrictive pattern even before treatment which has not worsened during the course of treatment. Patient had the same restrictive pattern even before and after treatment. Summarizing these, the Dose volume histograms for both Hybrid conformal and IMRT fields are as follows:

DOSE VOLUME HISTOGRAMS





7.DISCUSSION:

Treatment of Esophageal cancer is a challenging task for any radiation oncologist; treatment of any patient does not stop with patient alone, it goes a step further by rehabilitating the patient. It is because, Esophageal cancers, many of the times, are silent at early stages, usually providing vague symptoms like dyspepsia, belching, gastritis, dysphagia etc. The Classic symptom of dysphagia may not present initially, it usually presents at later stages and hence most of the esophageal cancers present late at diagnosis. Furthermore, local control, disease free survival(DFS), progression free survival (PFS), and overall survival (OS) at 2 and 5 years are usually less compared to other cancers. There is only a 20-30% overall survival benefit at 5 years with concurrent chemoradiation and less than 10% survival benefit with radiation therapy alone. Hence, expecting and treating side effects of therapy is a must which might improve the quality of life.

One of the most important and under looked side effect of radiation therapy in Carcinoma Esophagus is the incidence of Radiation induced pneumonitis. Radiation pneumonitis poses a significant challenge for any radiation oncologist whose treatment fields involve radiation dosage to lungs. Studies have always tried to find out the relationship and incidence of pneumonitis while irradiating the lung tissues either as primary, or secondary to

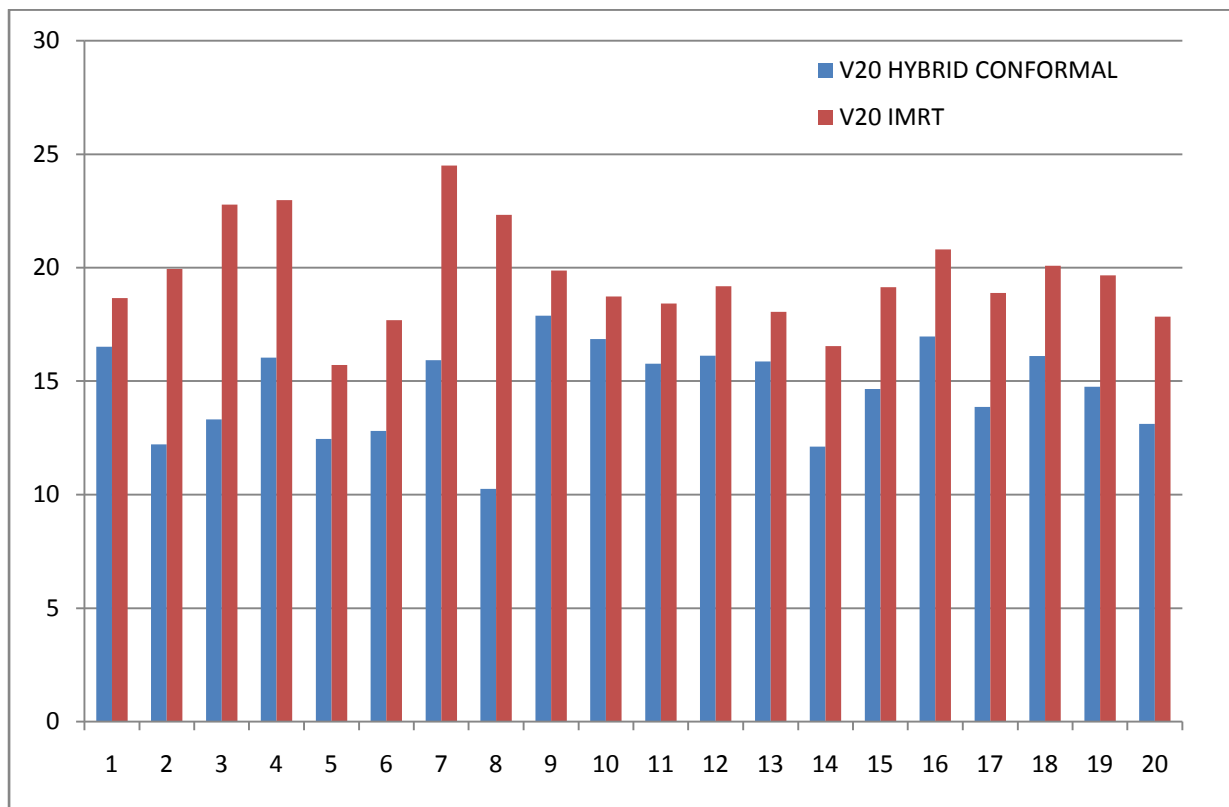
other carcinomas. Almost all the studies evaluated have shown that V20 values less than or equal to 30% is universally acceptable, according to QUANTEC dosimetric analysis, and hence, have always tried to maintain the lung dosage within such limits. Increased lung doses have been associated with increased incidence of radiation pneumonitis, though not in every case. There is an high chance of radiation pneumonitis in patients who undergo higher modern sophisticated techniques like the IMRT, due to the low dose to the normal tissues which interprets as increased lung dose. At the same time, dose to the tumour volume is better achieved with IMRT because, IMRT can be planned in such a way so that even in abnormal dose distributions, IMRT can achieve the homogenous uniform dose distribution that is expected.

Intensity modulated radiotherapy can achieve target dose better than conventional and conformal therapies; along with the reduction of normal tissue doses. Even though, the long term morbidity data for IMRT has to be proven because of the potential disadvantage of higher integral dose and irradiating low doses to the normal structures due to the various beamlets. Taking into consideration, Hybrid conformal therapy takes into account, combination of both conventional technique and conformal therapy. It is superior to conformal therapy alone in a way that the treatment for patient can be started as early as possible with two opposing anteroposterior and posteroanterior fields. Also, one of the approaches to treat esophagus has been the treatment of Hybrid

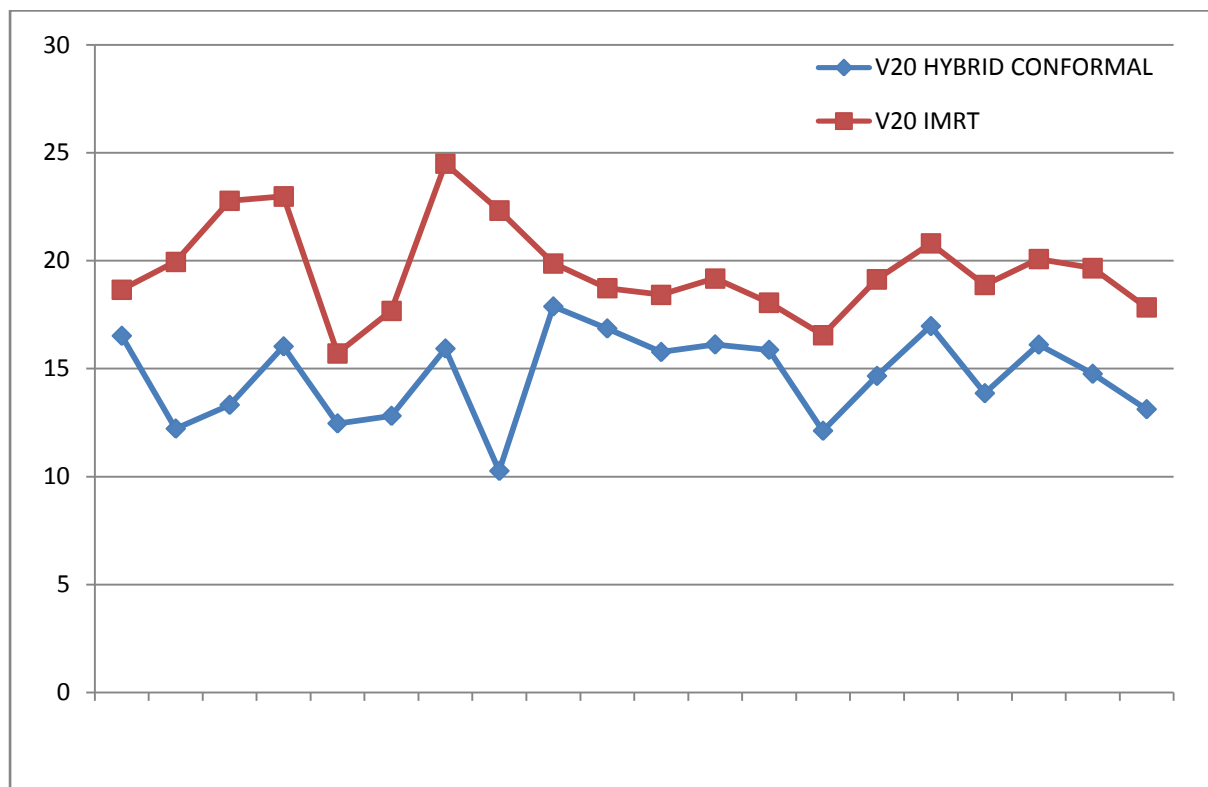
techniques with two opposing fields delivered upto half or two-thirds of total dosage, with the remaining doses being delivered either with conformal or IMRT techniques. This approach is followed because of the potential risk of myelopathy when the spinal cord is irradiated beyond 45 to 50 Gy.

Dose volume histograms comparing both Hybrid conformal and IMRT techniques in twenty patients suggest that tumour dose in Hybrid conformal technique achieved is not inferior compared to IMRT. Without compromising the tumour dose, the lung doses were calculated in both arms. The lung doses calculated with both the mean doses and V20 show that, in all twenty patients, V20 achieved is at least 5% lesser than that of IMRT; taking into fact that both these techniques achieve lung dosage constraint of less than 30 %. Similarly, mean lung dose achieved between these two techniques in all the twenty patients reveal that, doses achieved in Hybrid conformal technique is nearly one to two Gy lesser than that achieved in IMRT. This may be attributed to the fact that IMRT, even though is based on inverse planning, has larger beamlets and subfields, and hence delivers low dose radiation to normal tissues. This is particularly important, because of the fact that it might lead to an increase in the incidence of secondary malignancies.

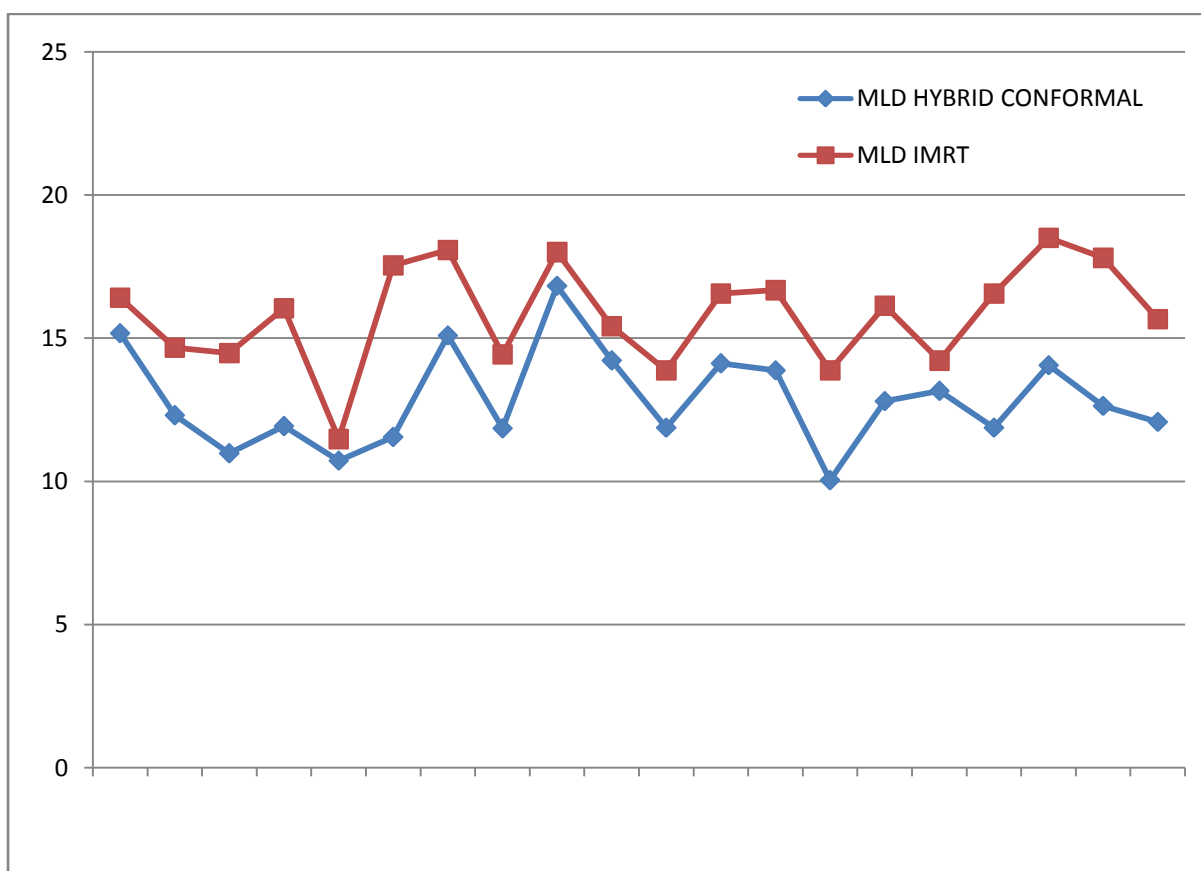
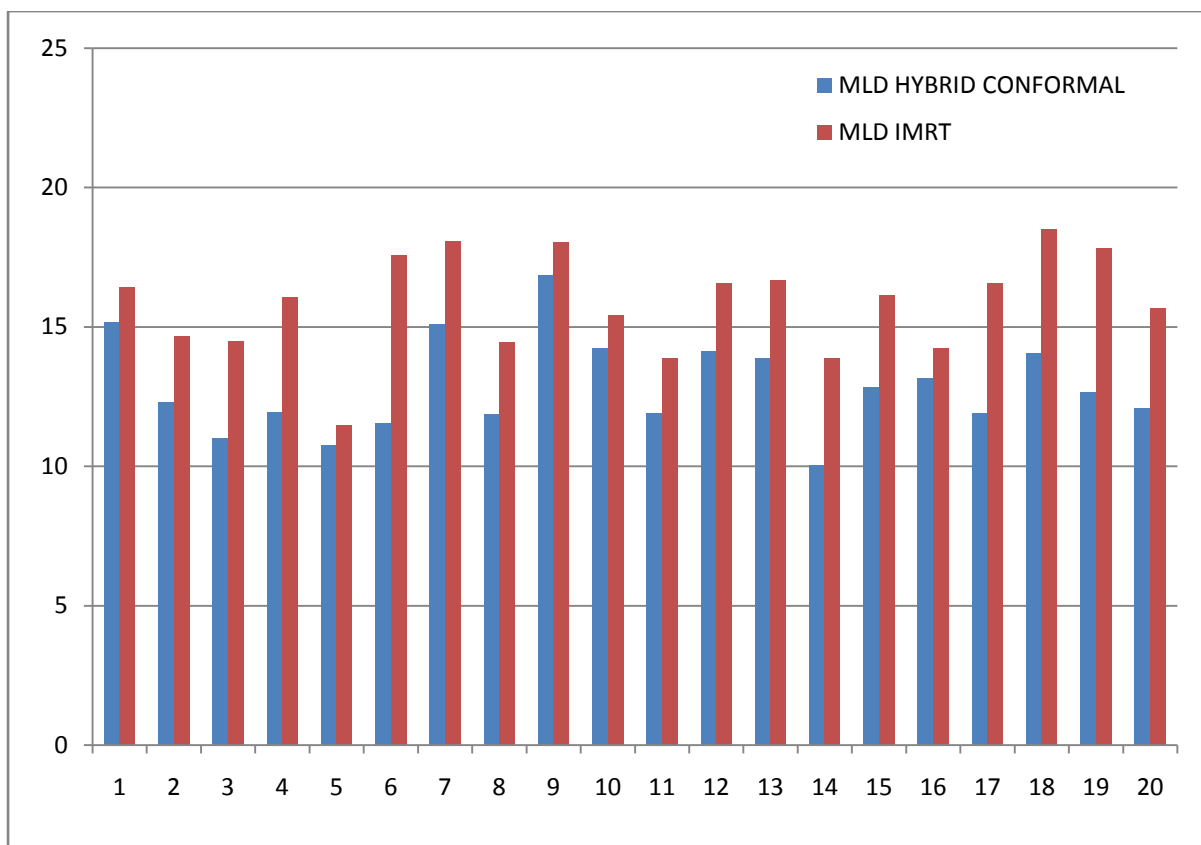
These values were statistically calculated to find out the statistical significance of the findings between both these arms. Both the mean dose to the lungs and volume of lungs receiving less than twenty Gray, were assessed statistically using independent t-test analysis, and it was found that the dose values in Hybrid conformal technique was lesser and was statistically significant compared to Intensity modulated radiotherapy with a p-value of less than 0.05. Hence, there was a significant difference statistically with the lung dose values trending towards a safer range with the technique under study, which might help in reducing complications. The following pictorial representation has dose percentage in y-axis and number of patients under x-axis, thereby comparing the V20 between Hybrid conformal and IMRT.



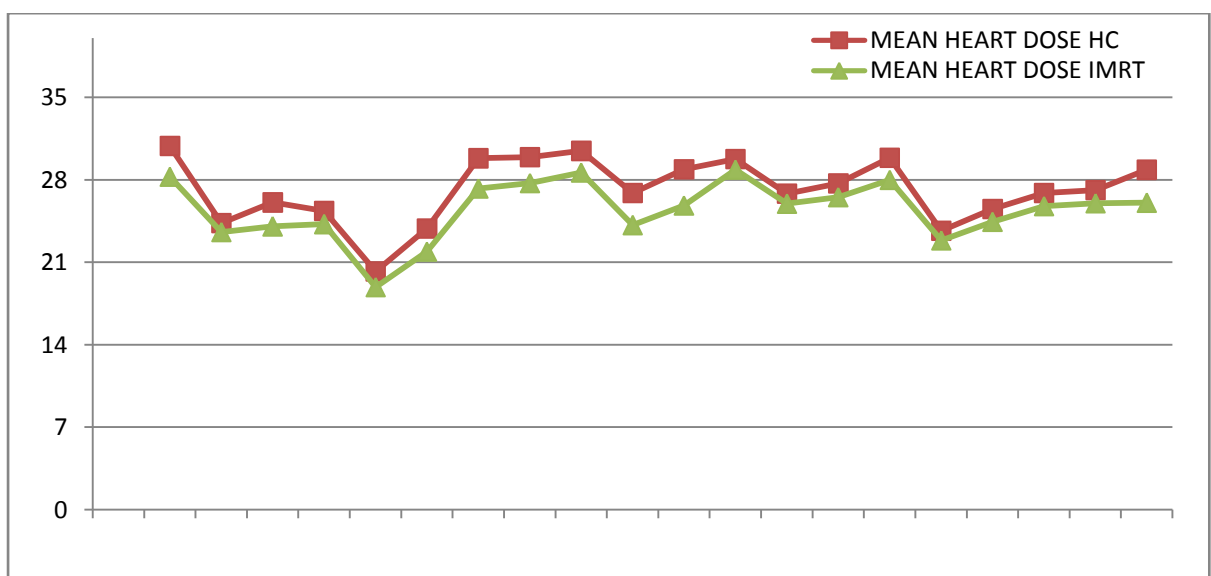
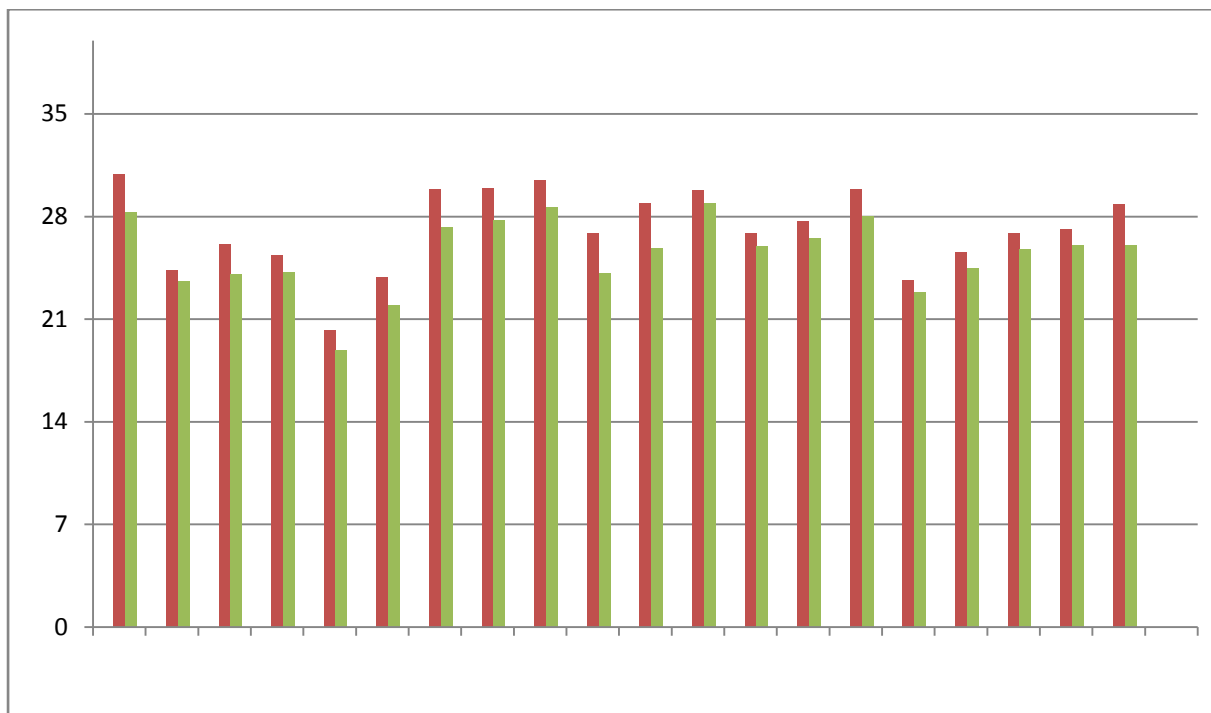
It can be better represented so that the V20 achieved will be comparable and is statistically significant. The blue line indicates the V20 values for twenty patients for Hybrid conformal technique and the red line indicates the same for IMRT.



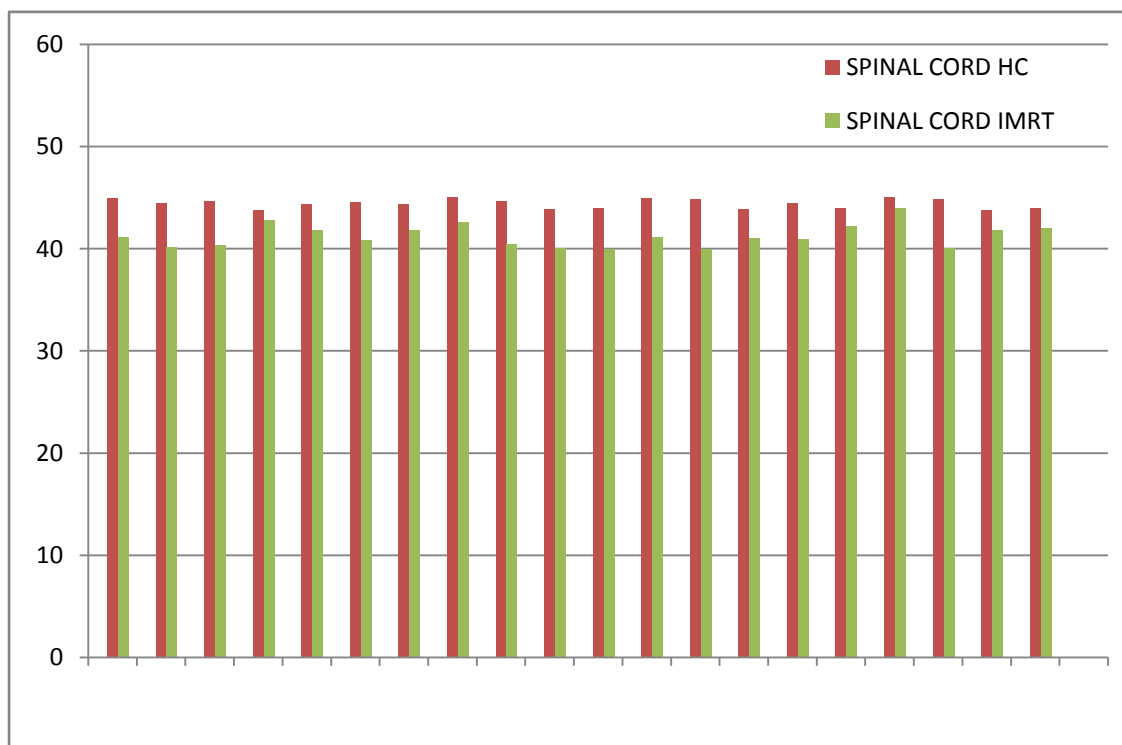
The mean lung doses for Hybrid Conformal technique and IMRT are given below in this bar diagram with x-axis representing the number of patients and y-axis representing dose values measured in Gray.

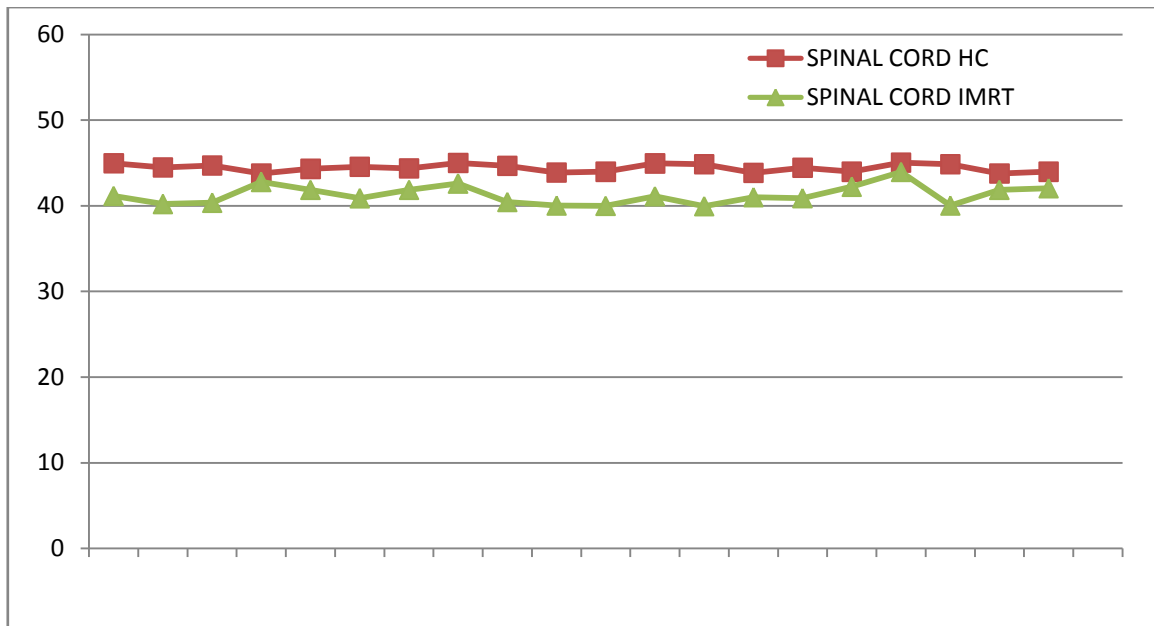


Mean dose to heart was also calculated between both Hybrid conformal and IMRT techniques. The values suggested that heart doses were lesser with IMRT compared to Hybrid conformal technique, but not significant to that of IMRT. It has to be seen whether the increased heart dose will present as pericarditis or other cardiac complications has to be seen.



Spinal cord dose constraint was kept into consideration in each and every patient, as the risk of developing myelopathy was always borne in mind, considering the fact, myelopathy is the deadliest complication that will paralyze the patient leading to disability thereby adversely affecting his or her quality of life. Both Hybrid conformal and Intensity modulated Radiotherapy techniques were planned so that all the twenty patients were receiving less than 45 Gy. IMRT plans achieved cord dose better due to its inverse planning, but was not very significant compared to Hybrid conformal technique. The latter was able to achieve the cord dose just like IMRT with just a higher margin, but within the constraint dose of 45 Gy. This significantly reduces the morbidity of increased cord dose, thereby keeping in line with the dose constraints.





The time taken for each technique was also noted. It was calculated starting from the entry of patient, to setup, and then deliver radiation till exit of the patient from the machine unit was assessed. The time taken for IMRT was around 17 to 20 minutes for each patient, compared to Hybrid conformal technique which took around 5 to 7 minutes for setup and delivery of the treatment. In the same context, two opposing, as expected, had lesser time duration than conformal technique, both of which, were much lesser when compared to IMRT.

Treatment delivery times usually are least considered when treatment modality is taken into account. But in places where daily patient turnover is very high, and the number of patients treated per day per machine is higher, treatment delivery times are considered to improve the efficiency and efficacy of treatment delivered. But at the same time, tumour dose volume should never

be compromised so that the patient is never under treated for his ailment. Reducing the time duration for each patient will considerably reduce the treatment times and hence patients can be treated without long waiting times.

Another factor for consideration of Hybrid conformal over IMRT is that, in Indian setup, many patients cannot afford the increased cost of treatment with IMRT. In such cases, a cheaper alternative that does not compromise tumor dose is required. Hybrid conformal technique will be fulfilling that fact and will be a very good alternative with additional benefits of sparing the lung volumes.

Pulmonary function tests used assess the function of lungs and to know about the severity of any lung impairment. Among the twenty patients studied, one patient had a restrictive lung pattern even before start of the treatment, and had the same value at the end of treatment. None of these patients had any incidence of pulmonary toxicity clinically, and hence at the end of treatment, almost all had the same values as pre treatment pulmonary function testing. There was no difference or change with the FEV1, FVC, Tidal volume or lung capacity with both pre treatment and post treatment testing. Even if pulmonary function testing done before and after treatment does not show any significant difference with Hybrid conformal technique, it cannot be confirmed that there is no incidence of radiation induced pneumonitis with Hybrid conformal, because,

pneumonitis is a clinical entity, and at least take around two to six months to develop post treatment. Hence, long term follow up data is required for both Hybrid conformal and IMRT technique to assess the incidence of pneumonitis, and pulmonary function testing at follow-up will be able to pick out the incidence of lung dysfunction at an earlier stage. To add to this, patients who are treated with irradiation whose treatment fields include lungs as organs at risk, pulmonary function testing can be made mandatory to assess the real incidence of treatment induced clinical symptoms of pneumonitis, which if done, can pick up earlier dysfunctions so that tackling of radiation induced pneumonitis can be easier for the treating physician.

One study (24) evaluated the incidence of radiation pneumonitis with increasing age. They compared younger age with advanced age patients with lung cancer, treated with irradiation involving thoracic fields. The study actually took into account 256 patients having both Stage I-III small cell and non small cell cancer, treated with irradiation with or without concurrent chemotherapy. The study showed that seventy patients were elderly, more than 70 years old and one hundred and fifty seven patients were less than 70 years old. Among them 30% of patients had grade II pneumonitis, 10% had Grade III pneumonitis and 1 to 2% of patients had Grade IV pneumonitis. The study concluded that Elderly patients are more vulnerable for radiation induced lung toxicity. Dose parameters like the V20, mean lung dose etc will help in assessing the toxicity,

but the threshold for clinical evidence of pneumonitis may be much lower than when compared with younger patients, matching other confounding factors available.

In another study (25), non small cell lung cancer patients who are treated with radiation therapy were taken into consideration and the risk of pneumonitis was noted. The study assessed the right parameter to assess the risk of radiation pneumonitis which might correlate clinically. It took into account 98 patients who were inoperable and were treated with definitive irradiation. Dose volume histograms were drawn and the parameters that are usually calculated like V5, V10, V20, mean lung dose, total lung volume, separate volumes etc are drawn and assessed. The risk of radiation pneumonitis especially Grade 2 pneumonitis increased steadily in these patients treated with irradiation. It was seen that, these patients had higher V20 values, was found to be statistically significant ($p < 0.05$) and it was concluded that V20 may be one of the main deciding parameter in evaluation of lung toxicity in patients treated with irradiation.

Similarly, a Chinese study evaluated the risk of therapy induced pneumonitis in non small cell lung cancer patients treated with concurrent chemoradiation. The study analyzed 220 patients treated with concurrent

chemoradiation and were followed up for a period of 10 months. It calculated the dosimetric analyses by using Dose volume histograms and calculated V5, V10, V15, V20 upto V60 in 5 Gy increments along with mean lung dose, lung volumes etc. The study correlated that incidence of radiation induced pneumonitis was evident with increase in V5 values itself. The results of this study also showed that values apart from V5, like V10, V20 etc also was associated with increase in incidence of pneumonitis. Analysis using multivariate logarithm showed that relative V5 values were associated with one year increased incidence of radiation associated pneumonitis. Many of these patients had Grade III pneumonitis, and the associated relative V5 value was kept to a value of 42%. Those patients who had a V5 of less than 42% had a 3% risk of radiation induced pneumonitis. On the contrary, the study reported that V5 value of more than 42% had a 39% increase in incidence of radiation linked pneumonitis. This led to the conclusion that relative V5 values are linked to a higher incidence of radiation induced pneumonitis, but may not be taken as the sole predictive factor until further evidences prove the same in randomized controlled trials.

One of the main study (26) that combined Hybrid technique was the study done in University of Massachusetts Medical school which compared Hybrid IMRT with other techniques. The study actually compared Hybrid IMRT that consists of static and dynamic beams which included IMRT technique for both

esophagus and lung cancer patients and to assess a way to reduce the volume of lungs treated with the technique along with delivering a conformal dose distribution.

This study took into account eighteen patients, twelve of which were lung cancers (both small and non small cell cancers) and six esophageal cancer patients treated between February 2005 to December 2006 spanning for a period of nearly two years. The study included static beams consisting of two opposing anteroposterior and posteroanterior fields for nearly two-thirds of dose and IMRT which included one third of dose given in combination that constituted the Hybrid IMRT. For comparison, the study took into account, conformal technique, a four field IMRT technique, five field IMRT technique, and a equally spaced nine field IMRT technique. The study carefully assessed the volume of lungs treated at different levels. This also included the naming of lungs as ipsilateral and contralateral; i.e, the lung that is receiving the maximum dose near the tumour was coined as ipsilateral and the opposite as contralateral lung volume. Dose volume histograms were drawn and was calculated for heart, lungs both ipsilateral, contralateral, total; and planning target volume. The plans calculated V5, V13, V20, V30 lung volumes, along with mean lung dose and Equivalent uniform dose.

Results of this trial showed that lung doses that were achieved with Hybrid IMRT were lesser, especially with V5, V13 and V20 volumes. It was

found that there was a larger reduction in this technique which combined static and dynamic beams that led to this reduction. Conversely, the comparison plans led to a higher lung volume, especially with V5 values which were reduced by 5 points in Hybrid IMRT. The V13 was reduced nearly by 3.5 points and the V20 volume were at least 11 percent lower than nine field sophisticated IMRT plan. Similarly, the volumes calculated, outperformed four and five field IMRT plans by a significant margin. But, conformal beam therapy led to lesser volume of lung being treated, but it was not statistically significant compared to Hybrid plans.

Finally, the authors concluded that treating patients with Hybrid plans and not an extensive IMRT plan, reduced the volume of lung treated due to the low doses imparted by the entry of beamlets with IMRT technique. This led to reduction of low dose lung volume to the lungs, that resulted in significant decrease of lung mean dose at least less than 13 Gy. This value was significant, as most of the studies compared and came to a conclusion that the values less than 13 Gy led to significant decrease in lung morbidity. Also, the authors tried their justification of their use of IMRT to one-third of dosage, because of the reduction of intrafraction motion that can be reduced only by gating, and hence reducing the error by means of using static beams to two-thirds of dosage. Finally, the patients under this study, did not encounter any radiation induced

morbidity that led to this technique, being non inferior to any of the other techniques that were taken into comparison.

The above mentioned study justified the superiority of usage of Hybrid techniques by means of four following explanations. They are as follows.

- ✓ Reduction of low dose lung volume that is a part of exclusive IMRT techniques. Hybrid techniques align the primary beams with two-opposing anteroposterior and posteroanterior axis, that led to the coverage of tumour volume. Hence, there was no compromise with the target volume, and IMRT boosted the primary beams thereby achieving a better tumour control, with reduction of lung doses.
- ✓ Secondly, dose errors due to patient motion. The thorax is the main site where motion due to respiration has to be taken into account. This leads to the fact, that IMRT plans, which have precise dose targets, will surely have intrafraction errors due to respiration. This can lead to under-dosage of target thereby leading to compromisation of tumour volume. This is reduced with Hybrid techniques, which reduces the IMRT planning thereby leading to reduction of these errors.
- ✓ Thirdly, the planning algorithms used in planning systems. It is found that, there is a greater error with beams that are highly sophisticated like

the pencil beams. IMRT uses such techniques, and these can be reduced further with Hybrid techniques.

- ✓ Fourth and not least, not every radiation oncologist are convinced with the IMRT plans, and due to the paucity of data that is available for their long term effects, and hence, this technique involves a plan that is between a conventional style and a sophisticated one.

Other studies like the presentation in American Society of therapeutic Radiology and Oncology (ASTRO) that held in 2004, showed similar results. This study assessed the risk of Radiation pneumonitis, which was mentioned with a grade 3 or more as classified by the Radiation Therapy Oncology group, by correlating with the dosimetric factors of heart, lung and its subregions.

This study retrospectively calculated and correlated the risk of radiation pneumonitis. Their patients had Grade 3 or more pneumonitis, and dosimetric analysis showed that V5, V10 and V13 to the ipsilateral and contralateral lungs were more linked with the risk of radiation pneumonitis. Hence the study concluded that, volume of lungs like V5, V10 and V13 were more linked with the risk factor more than V20, and hence concluded that incidence of radiation pneumonitis is more with these factors.

A chinese study (28) in 2005, analyzed the clinical and dosimetric factors that was associated with treatment related pneumonitis in patients with non small cell lung cancer. This study analyzed two hundred and twenty patients with non small cell lung cancer treated with concurrent chemoradiation. This study concluded that V5 volumes were more linked with the risk of therapy associated pneumonitis. V5 values less than 42 percent were associated with three percent increased risk which showed an increase to about 40%, when the same volume was associated with more than 42 percent.

Similarly, another chinese study assessed the incidence of postoperative pulmonary complications in patients with esophageal cancer by calculating the clinical and dosimetric factors who were treated with concurrent chemoradiation followed by surgery.

The above mentioned study took into account 110 patients with esophageal cancers treated from January 1998 to December 2003 over a span of five years. All patients underwent three dimensional conformal radiotherapy along with concurrent chemotherapy. Chemotherapy given was either 5-Fluorouracil or irinotecan based; with the radiation delivered upto a TD of 41.4 to 50.4 Gy. These patients then underwent surgery either by transthoracic or transhiatal esophageal techniques. The surgery was timed after thirty days upto 120 days

after chemoradiation. Dose volume histograms were drawn which calculated lung volumes, mean dose to lungs, mean dose to heart, etc. Endpoints were decided with the incidence of postoperative pulmonary complications like acute respiratory distress syndrome or pneumonitis that occurred one month after surgery. It was found that eighteen patients from the study group had incidence of radiation pneumonitis. All these patients, on retrospective analysis, found that, V5, V10, V20, mean dose to lungs etc were increased compared to the normal patients. The values associated with the increased lung doses were proportionate to the incidence of postoperative pulmonary complications. Also, compared to other volumes, V5 was associated with significant appearance of postoperative pulmonary complications. Hence this study concluded that, less dose to lungs, as evident by the reduced V5 values, might reduce the incidence of postoperative pulmonary complications.

Studies from the Mayo Clinic (25), tried to find out the dosimetric and clinical parameters that will be helpful to assess the incidence of radiation pneumonitis after radiation to the thoracic sites. This study analyzed retrospectively the incidence of Grade 2 or more radiation pneumonitis in patients with thoracic cancers. Dose volume histograms were drawn which analyzed Total lung volume along with the gross tumour volume, along with the MLD, V5, V10, V13, V20 and were calculated using regression analysis. Among the 92 patients studied, twelve patients presented with clinical

symptoms of radiation pneumonitis. Analysis showed that all these twelve patients had higher V5, V10, V13, V20, MLD, and Total lung minus gross tumour volumes. It was also seen that V10 and V13 were better predictors for radiation pneumonitis. The authors concluded that Intrathoracic radiotherapy should be cautiously and judiciously approached by the radiation oncologists while delivering a higher lung volume which are fraught with complications.

Studies from Japan (29) showed the causality between the incidence of radiation pneumonitis after twice daily hyperfractionation along with chemotherapy in patients with Stage III non small cell lung cancer. 37 patients were considered for this study and was treated with twice daily fractionation of 1.2 Gy upto a TD of 60 Gy along with chemotherapy which included paclitaxel and carboplatin regimens. Dose volume histogram was drawn and values were analyzed.

It was seen that, fourteen of thirty seven patients were having Grade II or worse pneumonitis. It was seen that all patients with V5 more than 40%, patients with V10 more than 35%, patients with V13 more than 33%, and V20 more than 24% were associated with increased incidence of radiation induced pneumonitis. The remaining patients had lower Vdose values and hence had lower incidence of pneumonitis. Also, the mean lung dose which was calculated

as more than 15 Gy in 8 patients were found to have more incidence of pneumonitis, compared to those patients who had less than 15 Gy had a lesser incidence of radiation induced pneumonitis. The authors concluded that these cut-off values will be more useful in assessing the risk associated with the incidence of radiation induced pneumonitis in patients treated with concurrent chemoradiation, even including hyperfractionation.

In this study, the dose to the planning target volume was calculated for both Hybrid conformal and IMRT techniques. It was seen that, the dose achieved by IMRT technique was superior, but at the same time, dose achieved by Hybrid conformal technique to the target volume was not inferior compared to the control technique. Moreover, the time taken for both these techniques to deliver treatment, varies significantly, as IMRT takes around 17 to 20 minutes to deliver treatment, whereas, Hybrid conformal technique takes about 5 to 7 minutes to complete the procedure. Hence, there is less waiting time compared and faster treatment delivery, which reduces the irradiation time to the patient.

The lung doses that is delivered via Hybrid conformal technique and the IMRT are compared extensively, where the volumes as well as the mean dose to the lungs are calculated. It is seen that, V20 received in Hybrid conformal technique was atleast 5 percent lower than IMRT which used seven fields. The

values achieved in these twenty patients were analyzed using independent t-test, and was found to be statistically significant with a p-value of less than 0.05.

Similarly, the MLD i.e. mean lung dose calculated in these twenty patients, were atleast one to two Gy lower in Hybrid conformal technique, compared to the seven to eight fields IMRT. This was also statistically analyzed using independent t-test, and was again found to be statistically significant having a p-value of less than 0.05. This proves that, Hybrid conformal technique, which is a mixture of static two-opposing anteroposterior and posteroanterior shaper fields for half the tumour dose, followed by conformal therapy by using three to four field technique for the reminder of the tumour dose. This in comparison, with an all-IMRT shows that, Hybrid conformal delivers much less dose to the normal tissue, whereas, IMRT delivers low dose volume to the lungs thereby resulting in higher integral dose, leading to higher V20 and mean dose to the lungs. This in turn, will reduce the theoretical incidence of secondary malignancies.

Furthermore, all these patients, underwent pulmonary function tests before and after treatment. Apart from one patient, the rest of the nineteen patients did not have a significant difference in their FEV1/FVC ratio. Even in that one

patient, who had changes, it was the same restrictive pattern both before and after radiation.

The result based on pulmonary function tests has two potential limitations: one, the test has to be done in follow-ups of one, two and six months, as the risk of clinical incidence of pneumonitis can be seen only after one to six months of radiation. Second, the test has to be done in IMRT arm, after delivery of the technique, which can show the true incidence of clinically significant pneumonitis. This in turn, has to be calculated for a period of before and after treatment, one, two and six months of follow-up.

Mean dose to the heart was also calculated, and it was found that, IMRT technique had a better chance of reducing the heart dose, but this difference was not significant when compared to that of Hybrid conformal technique, as the difference was low, and that, heart has a better tolerance limit compared to that of lung.

The dose to spinal cord was achieved in both techniques. IMRT, being a sophisticated technique, and a technique based on inverse planning, performs better in such cases to control the constraints. But at the same time, Hybrid conformal was able to achieve the same dose constraint, given the tolerance dose to spinal cord. Even though, IMRT achieved constraints like 40 Gy in one

case and 43 in another case, Hybrid conformal was able to achieve a constraint of less than 45 Gy in all cases, and hence the difference will not be statistically significant. Since this organ is based on series relationship rather than parallel, the dose constraint if less than 45 Gy is more than enough to prevent the incidence of myelopathy. Given the concept of reirradiation, at which point, IMRT doses are not much less compared to that of Hybrid conformal technique, and hence, won't be able to spare as much as cord as it is thought of.

8.CONCLUSION:

Hybrid conformal technique has potential advantages over IMRT such that it reduces the low dose volume to the normal tissues, thereby minimising the integral dose. It also eliminates the effects of patient's motion which affects IMRT in a great way, because, the margin for error in IMRT has always been very less. In Indian scenario, there is patient-cost factor which also plays a dominant part in deciding treatment modalities. In our country, not all patients can afford IMRT, and at the same time, IMRT is not justified in all patients, as many patients will not require such sophisticated techniques. In places, where techniques like Hybrid conformal can be used, it can virtually replace IMRT because of the potential reduction of side effects like radiation induced pneumonitis. This in turn, will reduce the incidence of postoperative pulmonary complications, which is usually reflected as pneumonitis and acute respiratory distress syndrome. Hence, this will lead to reduction of side effects, which ultimately reflects as better quality of life. Finally, there is a lack of potential data for long term side effects for IMRT. Till that is known, IMRT cannot be made the standard of choice, and hence, techniques like Hybrid conformal which has a better side effect profile and non inferior dose distribution with a better treatment time can be used, that will further avoid postoperative pulmonary complications. Even if the lung doses are avoided by Hybrid conformal technique, long term follow up data is required to assess the clinical

incidence of pneumonitis, which along with non inferior uniform dose distribution can be a boon to any radiation oncologist in the near future.

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Key Words:

Esophageal cancer, Hybrid conformal technique, IMRT, Two opposing and conformal therapy, Radiation pneumonitis, Treatment related pneumonitis.